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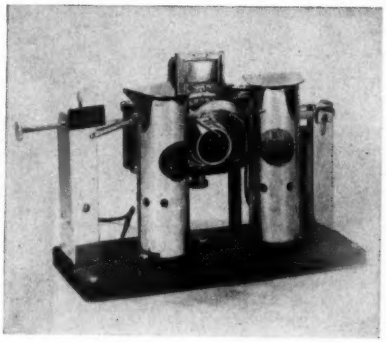

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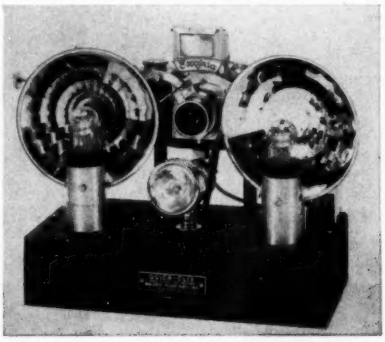

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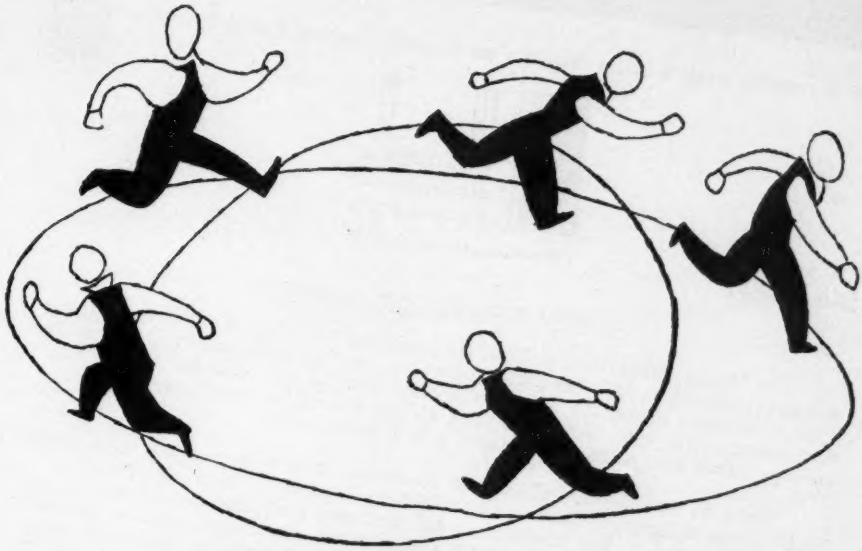

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1. Combes, F. C.: Coal Tar in Medicine. Industrial Medicine **13**:550-552 (July) 1944.
2. Combes, F. C.: Coal Tar in Dermatology. Arch. Dermat. and Syph. **56**:583-588 (Nov.) 1947.
3. Ellis, C. C.: Wooldridge, W. E., and Weiss, R. S.: J. Invest. Dermat. **10**:6 (June) 1948.

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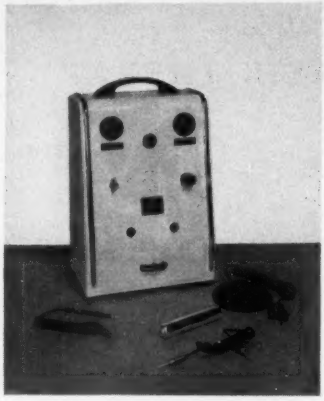

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Abdominal Surgery, Bancroft and Wade, 1947: 804

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Bulletin of the Johns Hopkins Hospital, Sept. 1948: 225-228
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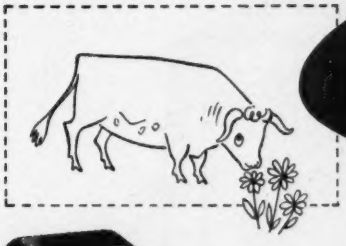

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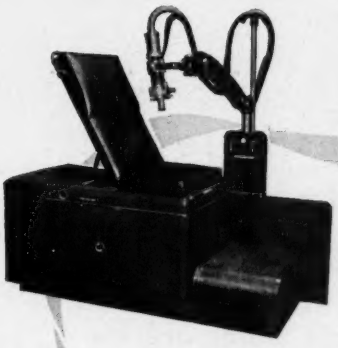

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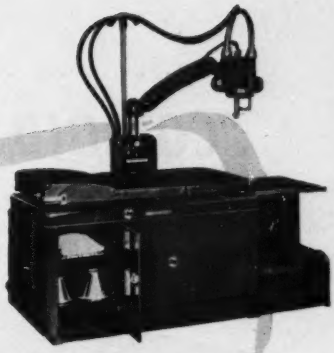

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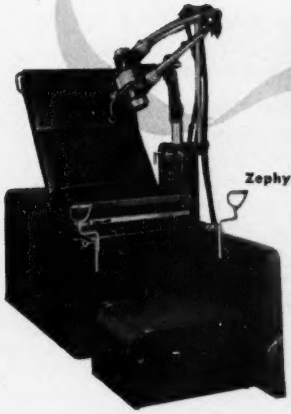

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CONTENTS

PAGE

"Chemical" Analysis of the Intact Skin by Reflectance Spectrophotometry. JOSEPH W. GOLDZIEHER, M.D.; IRENE S. ROBERTS, PH.D.; WILLIAM B. RAWLS, M.D., AND MAX A. GOLDZIEHER, M.D., NEW YORK.....533

Cortisone and Corticotropin (ACTH) in Treatment of Scleroderma. ROBERT R. KIERLAND, M.D., AND EDGAR A. HINES JR., M.D., ROCHESTER, MINN..... 549

Physiological and Chemical Changes in Radiation Injuries. FREDERIC T. JUNG, M.D., CHICAGO..... 555

Progesterone Therapy of Acne: A Clinical Evaluation. HENRY M. LEWIS, M.D.; GERALD M. FRUMESS, M.D., AND EGBERT J. HENSCHEL, M.D., DENVER..... 562

Evaluation of Chloramphenicol in the Treatment of Chronic Discoid Lupus Erythematosus. HARRY M. ROBINSON, M.D., BALTIMORE..... 565

Cortisone Acetate Administered Orally in Dermatologic Therapy. MARION B. SULZBERGER, M.D.; VICTOR H. WITTEN, M.D., NEW YORK, AND STANLEY N. YAFFE, M.D., BALTIMORE..... 573

Bismuth Putty in X-Ray Shielding: Efficiency of Material and Advances in Technique. J. WALTER WILSON, M.D., LOS ANGELES, AND RALPH LUIKART II, M.D., SANTA BARBARA, CALIF..... 580

Appraisal of the Toxicity of Sunscreen Preparations. J. H. DRAIZE, PH.D., WASHINGTON, D.C..... 585

Lichen Corneus Hypertrophicus (Lichen Ocreaformis, Lichen Obtusus): An Analysis of the Conditions with Which This Is Confused. ARTHUR B. HYMAN, M.D., NEW YORK, AND BENJAMIN D. ERGER, M.D., BROOKLYN..... 588

Antibiotic Sensitivity and Moniliasis. A. J. REICHES, M.D., ST. LOUIS..... 604

Podophyllotoxin Treatment of Microsporum Audouini Scalp Infections. C. JACK YOUNG, M.D., OKLAHOMA CITY..... 607

Congenital Ichthyosiform Erythroderma: A Report of Two Cases in Siblings, One Complicated by Kaposi's Varicelliform Eruption. WALTER C. FITZGERALD, M.D., DANVILLE, VA., AND ARMISTEAD P. BOOKER, M.D., CHARLOTTESVILLE, VA. 611

Lichen Sclerosus et Atrophicus and Related Disorders. CARL W. LAYMON, M.D., MINNEAPOLIS 620

Treatment of Urticaria and Dermatitis Venenata with Corticotropin (ACTH) and Cortisone. CAPTAIN GORDON H. EKBLAD (MC), U.S.N..... 628

CLINICAL NOTES:

Antihistaminic Lotion for Miliaria. DANIEL SCHULTHEIS JR., M.D., FLUSHING, N. Y., AND EUGENE F. TRAUB, M.D., NEW YORK..... 635

Contact Dermatitis of the Face Due to Matches. J. F. BURGESS, M.D., F.R.C.P.(C), AND R. ROY FORSEY, M.D., F.R.C.P.(C), MONTREAL, CANADA..... 636

Sinus Tract of Dental Origin. OTIS FIELD JILLSON, M.D., AND ROBERT H. PRESTON, M.D., HANOVER, N. H..... 637

Treatment of Folliculitis Keloidalis Chronica Nuchea (Acne Keloid). LESTER HOLLANDER, M.D., PITTSBURGH..... 639

(Continued on Next Page)

CONTENTS—Continued

PAGE

Allergic Stomatitis Due to "Baxin" in a Dentifrice. ALEXANDER A. FISHER, M.D., WOODSIDE, N. Y., AND MAXWELL LIPTON, M.D., ASTORIA, N. Y..... 640

Preparation of Slush. GARRETT A. COOPER, M.D., AND CHARLES W. STOOPS, M.D., MADISON, WIS..... 641

Stryker Frame in Treatment of Pemphigus. PARASKEVAS MICHAELIDES, M.D., AND MILTON REISCH, M.D., NEW YORK..... 642

Prevention of Hypersensitivity Reaction to Drug with Simultaneous Administration of the Drug and Cortone.® LEON GOLDMAN, M.D., AND EVELYN ROCKWELL, M.D., CINCINNATI..... 644

SOCIETY TRANSACTIONS:

Bronx Dermatological Society..... 645

Chicago Dermatological Society..... 648

San Francisco Dermatological Society..... 661

NEWS AND COMMENT..... 665

OBITUARIES:

Will Charles Davis, M.D...... 666

A. M. A.
Archives of Dermatology and Syphilology

VOLUME 64 NOVEMBER 1951 NUMBER 5

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"CHEMICAL" ANALYSIS OF THE INTACT SKIN BY REFLECTANCE SPECTROPHOTOMETRY

JOSEPH W. GOLDZIEHER, M.D.
IRENE S. ROBERTS, Ph.D.
WILLIAM B. RAWLS, M.D.
AND
MAX A. GOLDZIEHER, M.D.
NEW YORK

IT HAS been said repeatedly that one of the greatest obstacles to progress in dermatology is the lack of practical, quantitative methods for investigation of the skin. It is true, of course, that a number of good functional tests exist: measurement of sweating, sweat sodium, and lipid secretion, for example, is possible on a quantitative basis.[1] Skin elasticity can be studied in certain areas in a quantitative manner,[2] and such tests yield valuable information regarding some functions of the skin. In the main, however, quantitative investigation of the chemical or physical nature of the skin, and in particular investigation which leaves the same area of skin in a condition for further observation, is still a relatively unexplored phase of dermatology.

It is the purpose of this paper to present preliminary investigations of a method whereby a "chemical" analysis of the skin may be performed without in any way affecting or altering that tissue and thus making it useless for further serial observations. In the latter aspect alone it has a great advantage over histochemical techniques, microchemical analysis, ultraviolet microscopy, and other methods, for all these require an excised sample of skin. Such material is all too often unobtainable, particularly when serial studies are contemplated; even when it is obtainable, the very act of excision renders it "abnormal" in a certain sense and assuredly makes it impossible to do serial observations on that particular section of tissue. Therefore, a method which obtains information about a surface without in any way affecting that surface would seem to possess considerable advantages.

I. THEORETICAL BACKGROUND

One of the physical properties of any substance is its ability to absorb electromagnetic radiations of a specific wave length or wave lengths, and this pattern of

From the Research Department, St. Clare's Hospital.

Awarded honorable mention in the First Annual Essay Contest of the American Dermatological Association, 1951.

This investigation was supported by a research grant from the Division of Research Grants and Fellowships of the National Institutes of Health, United States Public Health Service.

1. Conn, J. W., and Louis, L. H.: J. Clin. Endocrinology **10**:12, 1950. Kirk, E.: J. Gerontol. **3**:251, 1948.

2. Kirk, E., and Kvorning, S.: J. Gerontol. **4**:273, 1949.

selective absorption is a fixed characteristic of that substance. When, for example, such absorption occurs in the range of visible light, "color" results. Thus, the absorption bands of oxyhemoglobin at 417, 548, and 578 mμ account for its red color, and the shift of the absorption bands to 431 and 565 mμ when reduced hemoglobin is formed accounts for the bluish-red hue of venous blood. Similar absorption phenomena can and do occur also in the ultraviolet and infrared ranges of the electromagnetic spectrum, and these patterns of absorption have been employed widely in chemistry and physics for the study and identification of specific substances. Most of the qualitative and quantitative tests in blood chemistry depend on "colors," i. e., specific absorption spectra whose intensities vary in proportion to the concentration of the absorbing substance. In the infrared spectrum there is even a zone called the "fingerprint region" because of the detailed evidence that these spectra yield regarding molecular structure.

It is clear, then, that an analysis of the absorption spectrum of a substance (or mixture) can yield considerable information as to its chemical nature and even as

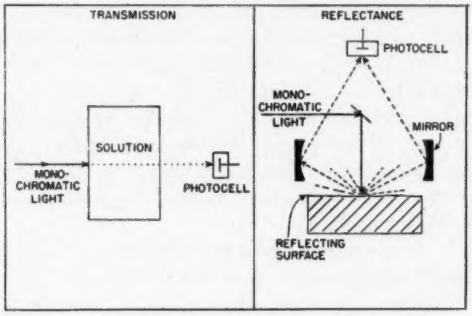

Fig. 1.—Comparison of the principles of transmission and reflectance measurement.

to the concentrations of the substances present. However, all the techniques mentioned so far require a clear, homogeneous solution of the substance in a "transparent" solvent; this is the actual situation in all common colorimetric procedures.

How, then, does this have any bearing on investigation of the skin, which is a somewhat irregular, semiopaque surface?

The property of "reflectance" of opaque surfaces is in many respects analogous to the "transmission" (which is the inverse of the "absorption") of homogeneous solutions. It is obvious that any surface may have "color" (i. e., specific absorption) in the same way as a solution, and this property should be capable of quantitative analysis in a manner analogous to the spectral absorption and transmission of a solution. In fact, the measurement of reflectance can be accomplished in a manner very similar to that used in the routine colorimetric study of solutions. This analogy can best be shown by an illustration (Fig. 1). It then follows that a "reflectance spectrum" can be established for opaque surfaces in a similar manner and with a connotation similar to the absorption spectrum of homogeneous solutions.

II. HISTORICAL DATA

It is necessary to dwell briefly on the development and previous investigations carried out by means of reflectance spectrophotometry.

Spectroscopic analysis is necessary for the exact determination of "color," and a number of attempts were made in earlier days to study the "color" of the skin by reflectance. These early attempts, hampered by great technical difficulties such as the intense heat of light sources and the poor electronic circuits available, are largely of historical interest. In 1939 a joint Harvard-Massachusetts Institute of Technology group, composed of E. A. Edwards, S. Q. Duntley, and subsequently others, reinvestigated the problem by means of the recently designed and very precise Hardy recording spectrophotometer.[3] This roomful of equipment is delicate and very costly (about $10,000), which may be one of the reasons why few people have been able to use it for investigative work. Moreover, its usefulness is limited by its optical system to the visible spectrum (400 to 700 mμ). With these advantages and limitations, Edwards, Duntley, and associates were able to accomplish significant work regarding skin color and skin circulation. The importance of their studies demands a brief summary of the salient features.

It was found that skin color was due to the combined effects of five factors: hemoglobin, melanin, a questionable pigmentary substance which was called "melanoid," carotene, and the scattering effect. (Scattering is the phenomenon which makes the sky overhead blue, the evening sky red; it is due to the differential dispersion of light as it passes through a nonhomogeneous medium.) Hemoglobin in its oxidized and reduced forms was identified in the reflectance spectrum by means of the characteristic absorption bands of these two forms; melanin extracted from Negro skin was found to have a diffuse absorption in the lower visible spectrum, and a corresponding depression of reflectance was found in the spectrum of the skin. By studying the spectra of skin areas on various parts of the body, "maps" could be made of the relative distribution of arterial and venous blood, melanin, carotene, and other substances. These workers, in a subsequent report,[4] were also able to show changes in skin circulation when, for example, the injection of testosterone caused an increased peripheral circulation and therefore a relative increase in skin oxyhemoglobin.

In studying the work of Edwards and associates, it appeared to us that many possibilities of this technique were as yet unexplored. For example, it is known that nucleic acids, important cellular constituents, show strong absorption in the ultraviolet region at 260 to 270 mμ; their distribution within single cells has been studied intensively by ultraviolet microscopy (Caspersson, Lavin, and others). Moreover, various aromatic amino acids (tyrosine, tryptophane) such as are found in tissue proteins have absorptions in the ultraviolet region. Thus, an extension of reflectance spectrophotometry into the ultraviolet region might possibly reveal information more vital than skin color and skin circulation. While the infrared spectrum held even greater promise, the technical difficulties encountered in this region were far too formidable for the facilities at our disposal. Moreover, there is no way at present by which one can circumvent the problem of expense in infrared

3. Edwards, E. A., and Duntley, S. Q.: Am. J. Anat. **65**:1, 1939.

4. Edwards, E. A.; Hamilton, J. B.; Duntley, S. Q., and Hubert, G.: Endocrinology **28**:119, 1941.

spectrophotometry, whereas it seemed possible that equipment within the practical financial range could be developed for visible-plus-ultraviolet spectrophotometry.

The problem thus resolved itself into the design of relatively inexpensive, portable equipment sufficiently sensitive and accurate to give useful data concerning skin reflectance in the visible and in the ultraviolet region, where reflectance is very low and the technical difficulties proportionately great.

III. TECHNICAL CONSIDERATIONS

Basically, three items were required. First, a table of appropriate size (on casters) was remodeled to support the spectrophotometer and accessory equipment. Second, a suitable spectrophotometer was chosen and "souped up" to fulfill the requirements of the work. Lastly, a technique of measurement with comparison to a standard reflecting surface had to be developed for the equipment and the problem at hand.

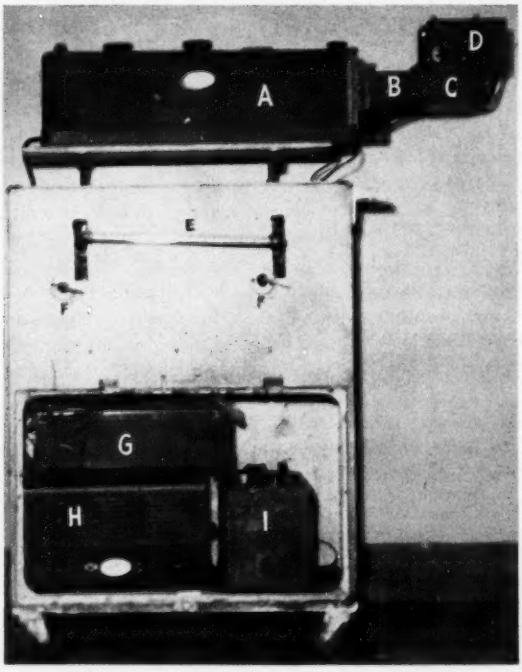

Fig. 2.—Spectrophotometer and accessory equipment used: the Beckman model DU has been reversed on its platform and the platform raised. *A* indicates spectrophotometer; *B*, extension arm; *C*, reflectance head; *D*, phototube compartment; *E*, hydraulic jack arm; *F*, bleeder valves; *G*, battery charger; *H*, ultraviolet power supply; *I*, battery.

1. An ordinary sterilizer table was chosen as starting material. Two small hydraulic automobile jacks were bolted to the shelf beneath the working surface, brought through openings cut in the table top, and then fastened to a platform of sheet metal heavy enough to support the body of the spectrophotometer (*A*, Fig. 2). The lever arms of the two jacks were connected together by a metal rod (*E*); gently pumping this rod up and down elevated the platform and

consequently the spectrophotometer. By manipulating the bleeder valves of each jack (*F, F*), one with each hand, the instrument could be lowered horizontally, or either end could be lowered independently. In this way a great deal of mobility was obtained without complex machinery. On the lowermost shelf of the table were stored the battery (*I*), the ultraviolet power source (*H*), and even the charger (*G*) used to recharge the battery. This assembly provided a means for wheeling the apparatus about, for bringing it to the bedside when necessary, and for raising it above and lowering it onto the area of skin to be studied.

2. The spectrophotometer selected was the Beckman model DU, a machine costing approximately one thousand dollars, but usually available in most institutions where biochemical research is done. This device has an interchangeable ultraviolet light source (hydrogen discharge continuous spectrum) of moderate power and a fairly good reflectance attachment as stock items. An 8-in. (20 cm.) extension piece (*B*) was machined to fit between the body of the spectrophotometer and the reflectance head so that it could be used on any chosen area of the body surface. The sensitivity of the instrument was increased by substituting a 10,000-megohm resistance in the phototube circuit for the one usually supplied and by making a more efficient quartz diffusion window in the reflectance head (discussed further in the appendix). These minor alterations, along with careful maintenance of the instrument, substantially increased its sensitivity and reliability.

3. Lastly, there were problems of measurement, concerning both the reference standard and the actual technique of measurement.

Measurements are customarily done with a fresh magnesium oxide film as reference standard, for this substance has a very high reflectance even in the far ultraviolet region (220 mμ). However, this film, prepared afresh each time by igniting magnesium turnings and collecting the smoke on a metal plate or disc, is a fragile and inconvenient object. Moreover, it has by the very virtue of its high reflectance a serious fault which obstructed other workers who (unknown to us) were experimenting along similar lines. The reflectance of the skin in the ultraviolet region is very low—of the order of a few per cent. Supposing at a given wave length (say, 250 mμ) the magnesium oxide film is set at 100% reflectance, and the skin is found to have a reflectance of 5%. At the next setting (say, 240 mμ) the magnesium oxide film is again set at 100%. If now the actual reflectance of the skin were 4.5%, this change could not be detected, because the technique is not accurate to better than 0.5% under these conditions. Yet, the relative change in the skin reflectance was from 5 to 4.5—that is, 0.5/5, or 10%. Thus, a large relative change may not be detectable when one compares a low-reflecting surface against a high-reflecting surface such as magnesium oxide. However, if one chose a standard which had relatively the same characteristics as the skin, then a high relative sensitivity would be maintained throughout (assuming sufficient instrument amplification). For example, if one set a low-reflecting standard at 100% at 250 mμ, the skin might show a reflectance of, say, 50%. With a shift to 240 mμ and a setting of the standard again at 100%, the skin would now show a reflectance of 45%—an actual change of 5%, and one easily measurable with adequate accuracy. By the simple expedient of using a standard of reflectance which has the general spectral characteristics of the skin, a considerable degree of accuracy can be achieved over the entire spectral range. This purpose was served by the use of a commercially available enamel plate; repeated tests determined its reflectance in terms of magnesium oxide with great exactitude, as there was no problem of absorption-band irregularities, and showed that it was entirely suitable for our work. The characteristic reflectance curve of an "80% neutral gray enamel" is shown at the left of Figure 3. In this manner, it became possible to measure the skin reflectance with sufficient accuracy from 250 to 700 mμ by comparison with an enamel plate and then, with the use of easily determined conversion factors, to express skin reflectance in terms of the standard reflectance of magnesium oxide. It also eliminated the repeated and troublesome preparation of magnesium oxide films. Determinations of the enamel plate over a three-year period have shown that its characteristics remained constant to a most satisfying degree.

The other major problem was that of comparing skin to enamel plate. Ordinarily, the standard and the unknown surfaces are placed in adjacent compartments of the sample holder; switching from one to the other is practically instantaneous. In skin measurements the sample holder has to be removed from the reflectance head, and it is obviously impossible to remove the machine from the skin after each wave length determination, reinsert the holder, and read

the enamel plate. Major changes of the reflectance head were not feasible at the time this work was started; therefore, another method had to be devised. The method selected is known as "memory standardization" and is frequently employed in infrared spectrophotometers or in other automatic devices which have great instrument stability. It was found that under optimal conditions, such as in battery charge and instrument maintenance, remarkable stability could be achieved with our equipment. This can be illustrated by the chart at the right of Figure 3, which shows successive measurements of the ultraviolet reflectance spectrum of the same person taken at 10-minute intervals. With such stability, it was possible to establish a fixed series of slit-width and sensitivity-control settings on the instrument for each wave length (hence, "memory standardization") and then to carry out a complete set of readings first on the skin and then on the enamel plate. Thus, two comparable sets of readings were obtained and the ratio of skin reflectance to enamel reflectance calculated; this figure was then converted by the previously determined factors into terms of magnesium oxide reflectance.

This method has been used very satisfactorily throughout the study; occasionally curves were encountered in which the instrument stability varied, and the effect on the plotted curve was instantly visible.

With these technical problems apparently solved, the method was ready for application to the study of human skin.

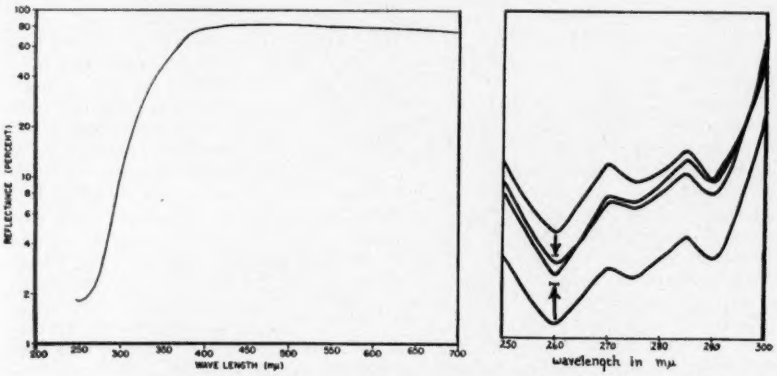

Fig. 3.—Left, reflectance spectrum of standard enamel plate (magnesium oxide film as absolute). Right, reproducibility study: Serial determinations of the same skin at 10-minute intervals. The upper and lower curves have been moved away from their actual positions (indicated by arrows) to clarify plotting. Note the close coincidence of curve level as well as curve shape.

IV. NORMAL SKIN: ITS REFLECTANCE SPECTRUM AND THE IDENTIFICATION OF SOME OF ITS COMPONENTS

Ten healthy young adult men and women were studied. For reasons not pertinent to this paper, only one area was selected for study, namely, the anterior or anteromedial aspect of the leg at midthigh level. All further observations will refer to this skin site.

A typical reflectance spectrum is shown above in Figure 4. The wave length of the incident light is plotted along the abscissa as usual. There are two ordinate (vertical) scales; this is necessitated by the low reflectance of the skin in the ultraviolet. Thus, in the region of 220 to 300 mμ the total vertical scale represents 0 to 10%; from 300 to 700 mμ the scale is 0 to 100%. In the study of this curve, which must be given detailed consideration, it is perhaps simplest to proceed from right to left—that is, from the red end of the spectrum toward the

ultraviolet. The various "dips" in the curve, representing specific absorption bands, have been labeled with fact and with conjecture; the latter is indicated by a

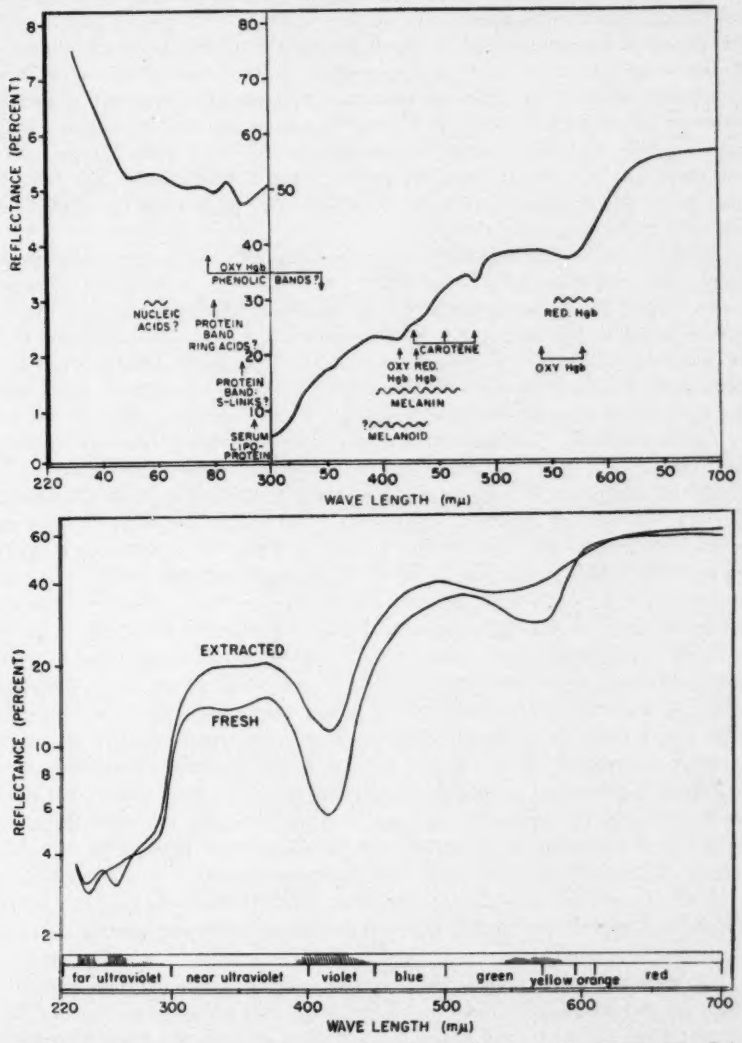

Fig. 4.—Above, reflectance spectrum of skin of normal woman (H. B. W., 26). Below, reflectance spectrum of healthy young aorta before and after ether-acetone extraction.

question mark after the notation. The first band encountered is a fairly broad one having its low point at 565mμ; this is typical of reduced hemoglobin, as has been shown in hemoglobin solutions by other workers and in

skin by Edwards and Duntley. The broad band indicates predominantly venous blood in this area, and because of its width, it obscures the lesser double bands made by oxyhemoglobin, which is undoubtedly also present in this area. At 485 and 455 mμ appear small bands probably due to the carotene which is found in the dermis and subcutaneous tissue. A broad band at 415 to 430 mμ represents further absorption characteristics of oxyhemoglobin and reduced hemoglobin, again indistinguishable at this particular skin site. The generally increased absorption (lowered reflectance) in this area is in some measure caused by melanin, which has no specific absorption bands but absorbs generally from about 470 mμ all the way down into the ultraviolet. It is therefore not a very suitable substance for analysis by this technique, although useful data can be secured by serial determinations under exact conditions.

In the ultraviolet, a region not explored previously, a number of bands are found. The near ultraviolet, from 400 to 300 mμ, shows some band formation, possibly Soret bands, but technical difficulties and insufficient data on absorption characteristics in this range have so far prevented us from successful analysis of these findings. The "far" ultraviolet, from 300 to 250 mμ, has been attacked more successfully. A search through the literature of absorption spectra has given some clue as to the substances most likely to show up in this region, and they are indicated with question marks. Our major problem has been to identify these bands, having the observed skin curve and these various possibilities as the starting data. The manner in which this may be done is illustrated, for example, in identification of the very prominent band seen at 290 mμ. Consideration of the available facts suggested that the presence of sulfur-bearing amino acids and proteins might be the explanation of this phenomenon. Since keratinous substances are rich in sulfur, this seemed to be a worth-while hypothesis. To make certain, however, that this absorption band was not due to a general protein phenomenon, a sulfur-poor protein was first selected for study. Elastic tissue seemed to be a fairly suitable choice, particularly as it is one of the more important components of the skin. At first the only such material available was healthy young aortic wall. This tissue gave the curve shown below in Figure 4. The two hemoglobin bands are very prominent, as might be expected. There is no absorption at 290 mμ, even after ether-acetone extraction, which would remove any interfering lipid substances present but would not alter elastin. Subsequently we were fortunate in being able to examine two specimens of pure elastin, prepared from young and old persons by Dr. A. I. Lansing of Washington University. The reflectance curves of this material (Fig. 5, above) showed no absorption at 290 mμ. Thus it was fairly safe to conclude that the absorption band in this region does not indicate some general molecular characteristic of protein.

The next step was to prepare homogeneous samples of different types of keratin. Finely ground scrapings from clean, healthy fingernails served as a sample of hard keratin; dried and pulverized heel callus served as an intermediate and pigmented keratin, and dandruff washed free of oils with ether and centrifuged to separate it from inorganic dust and dirt supplied a sample of soft keratin. Exfoliated material from a case of sunburn was also used and gave results identical with dandruff. The reflectance spectra of these three types of keratin were determined, as shown below in Figure 5.

Heel callus shows the characteristic absorption band of carotene (and possibly "melanoid") in the visible violet (maximum at 430 mμ), but otherwise all these materials show little of interest in the visible range. Hard keratin (nail) and heel callus show no definite absorption bands in the ultraviolet; the rise between 250 and 220 mμ is a calibration artefact and should be ignored. However, soft keratin

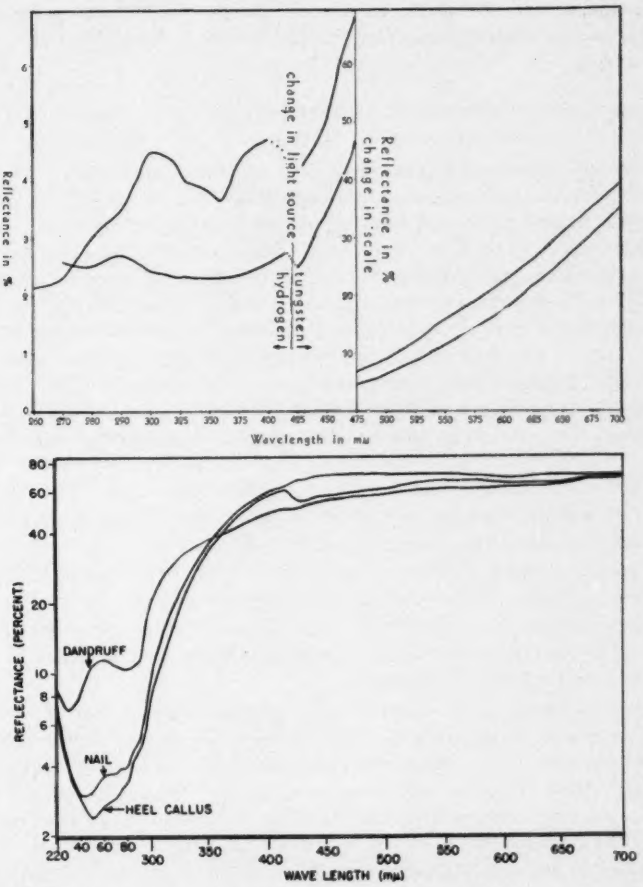

Fig. 5.—Above, reflectance spectrum of isolated elastin obtained from young (lower curve) and old (upper curve) aortas (the material was furnished by Dr. A. I. Lansing). Below, reflectance spectra of various types of keratin.

shows a very definite absorption band in the 280 to 290 mμ region. Search through the spectra of other substances found in appreciable concentration in the skin fails to indicate anything else that might give this band, with the one exception of hemoglobin, which has some absorption at 270 to 280 mμ. The evidence obtained

so far is suggestive, but it still remains to be proved that soft keratin, perhaps including keratohyalin granules, is the substance which is identified by the 290 absorption band.

To obtain further evidence on this point, it was decided to study very thin, atrophic skin and see whether there was a diminution of the 290 band commensurate with the lack of soft keratin and, furthermore, to see if in the course of regeneration of this skin, an increase of the band would parallel the increase in keratohyalin granules and keratinized cells. The possible role of oxyhemoglobin also required investigation.

V. SENILE SKIN: COMPARISON OF HISTOLOGY AND REFLECTANCE SPECTRUM DURING HISTOLOGICAL ALTERATIONS OF THE SKIN

Forty-one serial experiments were done in which ether-alcohol solutions of steroids were sprayed twice daily onto senile skin for 45 consecutive days, and spectrophotometric curves and biopsies were taken at 15-day intervals. The histological material was fixed in dilute Bouin's fluid, embedded, and sectioned. Only the data from hematoxylin-eosin and picrocarmine-stained sections will be discussed here. Slides from each series were marked in time sequence and were then coded, so that the histological examination and evaluation, performed entirely by one of us (M. A. G.), was done completely without knowledge of the substance used on the skin or of the results of spectrophotometry. Also, the reflectance curves were interpreted (in writing) with no knowledge of the histological findings. Only when the data of these two techniques had been assembled completely were they compared. In 33 of 36 series the conclusions as to the changes in keratinization and keratohyalin formation coincided with both techniques.

A few specific examples will illustrate the results. Figure 6 shows the far ultraviolet reflectance spectrum measured at 0 days and after 15, 30, and 45 days of therapy. Examining the 290 mμ band only, it is quite evident that no consistent alteration has taken place. The histological study showed, "no change in the histological appearance of this atrophic skin. No increase in keratohyalin granules," and other evidences of no alteration. In keeping with the atrophic nature of the skin is the low amplitude of the 290 band.

Figure 7 illustrates the complete reflectance spectrum of another senile skin. In the far ultraviolet spectrum the "control" curve shows very little in the way of absorption bands; this one would interpret as an atrophic skin with little keratinized material. Under treatment, the absorption band at 290 mμ is seen to increase sharply and progressively, and this would be interpreted as an increase in soft keratin and keratohyalin material. The histological changes were entirely in accord with this interpretation, as shown by the picrocarmine stains in Figure 8. The histological report stated further that the control skin was thin, atrophic, with a flat basal layer of epidermal cells and few rete pegs; this gradually reverted to a more normal aspect with thickening of the epidermis and appearance of more numerous papillae in subsequent biopsies.

This particular case also affords fairly conclusive evidence on a point which has been passed over momentarily—namely, that the 290 band might simply represent an oxyhemoglobin absorption band. Examination of the hemoglobin bands in the visible spectrum at 417 to 430 and at 565 mμ shows that the absorption due to

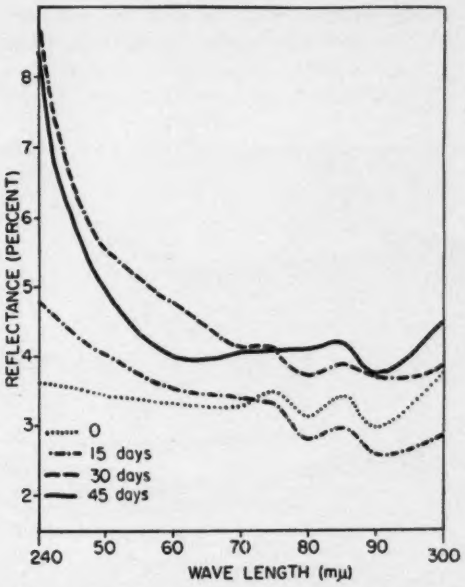

Fig. 6.—Ultraviolet reflectance spectrum of man (Dan, 63) treated with estrone, 2 mg. a day, with no oil carrier.

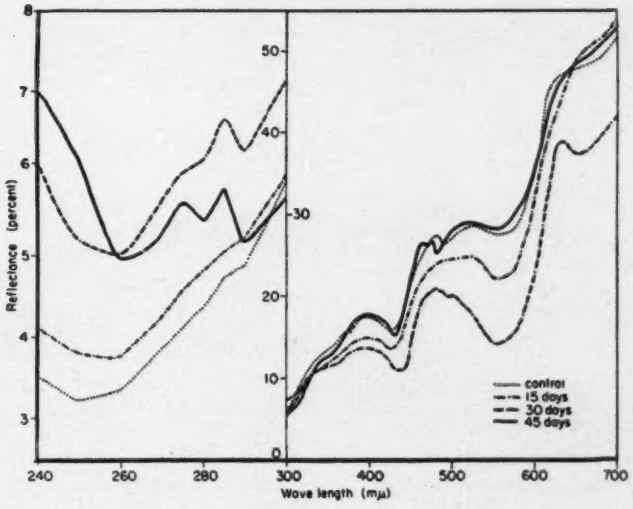

Fig. 7.—Reflectance spectrum of woman (Moo, 70) treated with testosterone plus an oil carrier, 5 mg. a day.

this material is practically identical before the beginning of treatment (0 days) and at the end of 45 days. The curves at intermediate times show intermediate but not progressive values. These alterations apparently indicate only temporal differences in the amount of venous blood in the skin. If the 290 band were also a hemoglobin

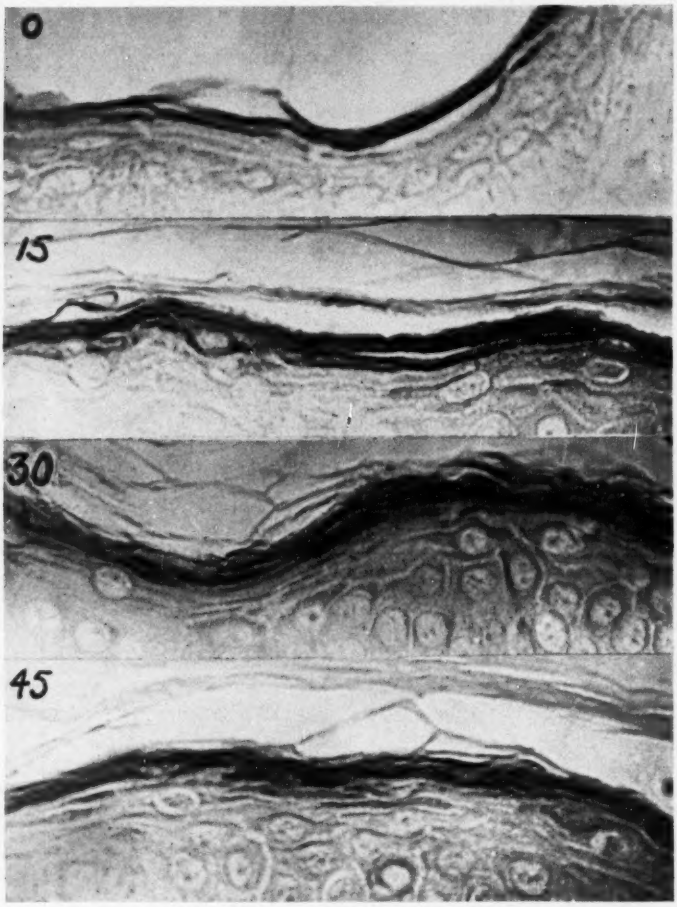

Fig. 8.—Changes in senile skin, at 0, 15, 30, and 45 days of treatment, showing increase of soft keratin and keratohyalin material (reflectance spectrum of this skin shown in Figure 7).

absorption phenomenon, it would have to vary in a manner similar to these other (visible) absorption bands at 417 to 430 and 565; in fact, it does not. The lack of correlation of changes in 290 absorption with hemoglobin bands elsewhere, on the one hand, and the good correlation of changes of 290 absorption with histological variations in soft keratin, on the other hand, constitute fairly good evidence that

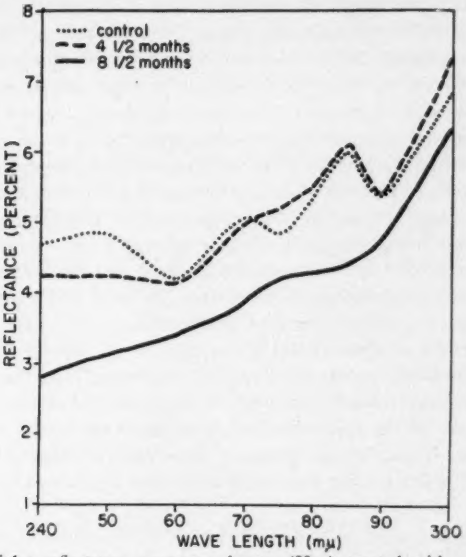

Fig. 9.—Ultraviolet reflectance spectrum of man (Hor) treated with estrone plus an oil carrier, 9 mg. a day.

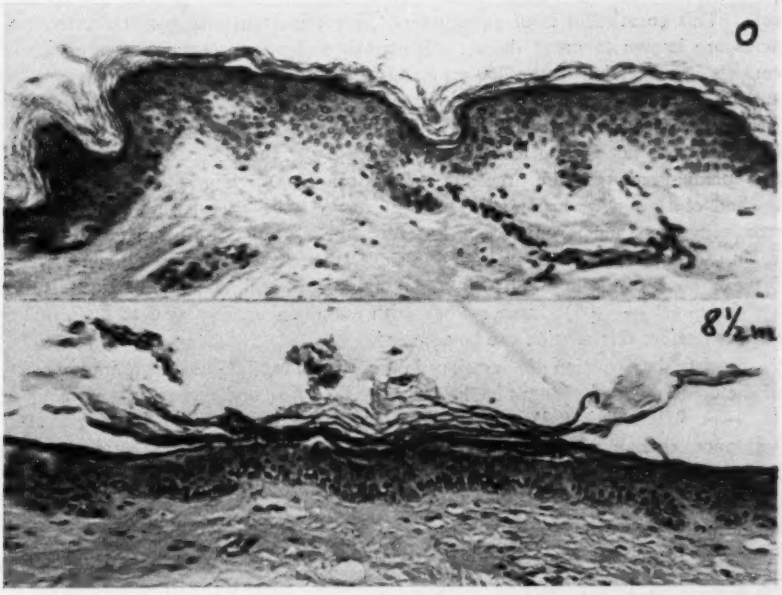

Fig. 10.—Senile skin at start of treatment and after eight and one-half months of treatment; atrophy of the epidermis had occurred during the course of intensive and prolonged therapy (reflectance spectrum of this skin shown in Figure 9).

this band represents the existence and concenrtation of keratin and keratohyalin material in the skin. Figures 7 and 8 also illustrate the fact that quantitative alterations in this material can be observed in serial spectrophotometric studies.

A final case will serve to illustrate the manner in which other types of progressive change can be followed. Figure 9 reproduces only three of many curves obtained in an aged person who was under observation and treatment for a period of eight and one-half months, during which extremely large amounts of steroid were sprayed on the skin. Analysis of these curves was very puzzling, because the 0-day (control) curve showed a fairly substantial absorption band at 290 (and also at 275 and 260 mμ), and these bands gradually diminished with time. At four and one-half months, the 275 mμ band had virtually disappeared and the 260 band had diminished; at eight and one-half months even the 290 band had flattened out. Such very flat curves had been associated with thin, atrophic epidermis in our hypothesis, and the interpretation of these findings was that things seemed to be going backward instead of forward. It was gratifying to receive the report of the histological findings (Fig. 10) and to learn that, whereas the control skin was fairly normal in appearance, atrophy of the epidermis had occurred in the course of intensive and prolonged therapy. Thus the significance of these reverse changes became immediately clear and afforded further corroboration of our hypothesis.

VI. FURTHER STUDIES

After apparently successful identification of one constituent of the skin, work is now in progress in an attempt to correlate the 260 absorption band with the presence and concentration of ribonucleic and desoxyribonucleic acid within the cells. This constituent is of great interest, for important changes in the nucleic acids are known to occur during cell growth and neoplasia. The present work consists in evaluation of the 260 mμ band in the reflectance curves and independently a study of the nucleic acids in the cells by means of special stains of the biopsy specimens. Up to the present time, the Turchini method of staining, as described by Glick,[5] has not proved satisfactory, nor have the stains currently available for the methyl-green-pyronin procedure yielded usable preparations. The Feulgen method of staining, when applied to tissue fixed with Bouin fluid, shows great variability of staining from section to section, making quantitative estimates unreliable. Although statistical examination shows that there seems to be a correlation between signs of proliferation (on hematoxylin-eosin sections) and changes in the 260 band ($P = 0.05$), further work with successful nucleic acid stains will be required before this relation can be accepted.

Statistical correlation of alterations in the 275 mμ band with changes in thickness of the epidermis and changes in the number of papillae and rete pegs is very good ($P = < 0.01$ and < 0.05 respectively); it remains to be shown what particular substance, changing as it does during cellular proliferation, this absorption band represents.

Other technical problems are also under consideration. Slight changes are being made in the reflectance head with the hope that its efficiency will be increased; an improved ultraviolet source, with 50 times the output of the Beckman tube, has

5. Glick, D.: Techniques of Histo- and Cyto-Chemistry, New York, Interscience Publishers, Inc., 1949.

recently been developed by the Jarrell-Ash Co. of Boston; this would increase the sensitivity of ultraviolet analysis by at least one order of magnitude (possibly by a factor of 50) and allow for extended investigation even further into the ultraviolet. We hope some day to extend the investigation to the infrared region if funds should become available.

The studies discussed here are limited to the normal skin and extended only to one type of pathological change, i. e., senile atrophy. This limitation has been purposeful: it was felt that the technique of reflectance spectrophotometry had to be developed and shown to be practicable and useful for investigation of as yet unknown properties of the normal integument. Only then could other problems be attacked profitably. There is an entirely unexplored field ahead in the study of skin pathological change by reflectance analysis. Skin lesions and malignancies, the effect of various types of radiation, the accumulation in the skin of dermotropic substances (provided they have suitable spectral characteristics or effects) are all capable of investigation by this method. The existence and possibly the concentration of a vast variety of substances, both normal (as for example, aromatic amino acids) and abnormal (possibly such as heavy metals, and various drugs), are capable of similar analysis. The three basic criteria which have to be met are (1) satisfactory spectral characteristics; (2) absence of masking by other constituents; (3) adequate concentration in the tissues. That these requirements are far from insuperable has been demonstrated, we believe, by the studies just described.

SUMMARY

A practical apparatus has been developed for the analysis of the skin reflectance spectrum in the visible and in the ultraviolet region, using equipment within the reach of the average institutional budget.

A technique for measurement in the ultraviolet range has been developed which permits satisfactory accuracy at low levels of reflectance.

The existence in the skin spectrum of characteristic bands due to oxyhemoglobin, reduced hemoglobin, carotene, and melanin has been confirmed.

The ultraviolet spectrum has been explored and the study of keratin and its identification in the skin ultraviolet spectrum demonstrated.

Progressive alterations of a skin component (keratin) have been followed by this technique and the conclusions verified by correlation with independently studied serial skin biopsies.

The direction of further studies has been indicated and the general scope and possibilities of the method discussed.

TECHNICAL APPENDIX

Certain difficulties were encountered in our attempt to use the standard Beckman model DU spectrophotometer and its accessories for the work which has been described. A number of minor alterations and tests of the instrument's properties were found useful.

Electronics.—Substitution of a 10,000-megohm resistance in the photoelectric cell circuit was found to increase the sensitivity and the precision. Otherwise, no alteration of the electronic circuit was considered, as a further increase in sensitivity would have required photomultiplier tubes instead of phototubes. This would be a major and costly alteration of the electronics—exactly the sort of thing we wanted to avoid. Phototubes were carefully selected to assure maximum steadiness.

Reflectance Head.—The efficiency of the quartz diffusion window in the reflectance head was studied. This is the area on which the reflected light is focused and then "inspected" by the phototube. Obviously its transmission and dispersion are critical factors in the efficiency of the instrument. When the standard 4-mm. thick sintered quartz disc was replaced by a 1-mm. fused quartz disc ground rough on one side and smooth on the other, a 77% increase in the amount of light energy available to the phototube was obtained.

Reflectance Standard.—It was found that magnesium oxide films could be prepared most satisfactorily by placing a tablespoonful (15 cc.) of magnesium turnings in a heap on an ordinary square metal gauze such as is used over a bunsen burner. The asbestos center was first heated thoroughly over a bunsen flame to burn away as much combustible material as possible; then the gauze was allowed to cool, turned asbestos-side up, and the turnings placed on the asbestos and ignited with a bunsen flame. When the burning magnesium formed a solid ball of fire, the rising smoke was usable. An enamel plate 1 by 3 in. (2.5 by 7.7 cm.) was grasped at one corner with a pair of forceps and held at a 45-degree angle in the rising smoke column about 4 in. (10 cm.) above the flame. A little experience was required to get a sufficiently thick (about 0.06 in. [0.15 cm.]), yet smooth, surface. This standard was then inserted in one compartment of the reflectance sample holder and a neutral gray enamel plate in the other compartment. The reflectance curve was then determined in the usual manner. The average of 10 such comparisons, each with a fresh magnesium film, was taken as the value for the enamel plate. Subsequent rechecks over a period of three years showed no detectable alteration in its characteristics (Fig. 3).

Measurements.—The technique of memory standardization stands or falls with instrument stability, a state often difficult to achieve; hence, much thought has been devoted to elimination of this type of measurement. With the assistance of Dr. N. A. Finkelstein, a simple modification of the reflectance head has been designed. A slot is cut in the side of the head and two runners built within it, so that the standard enamel plate is kept inside the head and is held in a position directly under the light beam by means of a spring. The other edge of the enamel plate is connected to a rod which forms the movable core of an electromagnet mounted outside the reflectance head. When this solenoid is energized by an electric current (a foot pedal can be used for a switch), the enamel plate is pulled away from the light beam, allowing the unknown surface to be measured. Release of the switch again positions the enamel plate. Thus the usual type of measurement by "instantaneous" comparison is possible, and the problem of instrument stability is made minimal. This device is well within the technical facilities of the usual institutional or small commercial machine shop.

Extension Arm.—The reflectance head had to be extended out from the main body of the machine so that all parts of the body could be reached if desired. This rectangular casting is illustrated in the figure of the apparatus (Fig. 2) and is also a very simple machine-shop assignment.

Light Source.—Finally, there arises the problem of the accuracy of measurements in the ultraviolet range. Because of the low light intensity available from the stock tube supplied with the instrument, a wide band of ultraviolet light had to be used (4 to 8 mμ). The two ways to obtain usable and more monochromatic light would be to increase the instrument sensitivity (not feasible, as discussed above) or to increase the power of the source. The Jarrell-Ash source mentioned above is about 50 times higher in energy output than the one now being used. This would supply ample light energy so that highly monochromatic radiation could be used to analyze the skin. It must not be thought that such an increase in source intensity would produce radiation which might affect the exposed surface: the total radiation to which the skin is exposed would be increased very little, but its monochromatic characteristics would be greatly improved.

No mention has been made of automatic recording devices because these instantly raise the cost of the apparatus to prohibitive levels.

CORTISONE AND CORTICOTROPIN (ACTH) IN TREATMENT OF SCLERODERMA

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A WIDE variety of supposedly unrelated diseases have been treated with cortisone, among them the so-called collagen group of diseases. It was natural, then, that cortisone should be administered to patients who have scleroderma. Four such patients, all women, have been treated at the Mayo Clinic. The results achieved form the basis of this report.

REPORT OF CASES

CASE 1.—A 25-year-old white woman first came to the clinic in October, 1949. She said that beginning in the summer of 1946 she had noticed a swelling and firmness of the fingers unassociated with any other symptoms. In the fall of that year painful, scaly, crusted lesions developed on the finger tips. At the same time, she also noticed the color changes of Raynaud's phenomenon upon exposure to cold. Symptoms gradually increased until April, 1948, when she became pregnant. During her pregnancy the symptoms spontaneously abated an estimated 75%; however, in April, 1949, after delivery, the symptoms recurred. This association of spontaneous improvement during pregnancy led us to the thought of administering cortisone. The progression of symptoms continued: The patient's face became taut, there was limitation of the motion of all the joints of the extremities, and she was unable to do simple tasks, such as tying her shoes, combing her hair, and dressing herself easily, as she had been able to do in the past. A diagnosis of "moderately advanced acrosclerosis with Raynaud's phenomenon" was made.

The original laboratory examinations had disclosed normal results of urinalysis, normal amounts of hemoglobin, erythrocytes, and leucocytes, and a normal differential count. The sedimentation rate was 19 mm. in one hour (Westergren). In addition, the values for urea and sugar in the blood, and proteins, sodium, and potassium in the serum, were within normal limits. Roentgenologic examination of the thorax revealed only healed Ghon tubercles. Roentgenologic examination of the esophagus revealed scleroderma of the esophagus, with loss of peristaltic activity in addition to some stiffening of the esophagus. Dental roentgenograms demonstrated widening of the periodontal membranes of the bicuspid and lower teeth. In addition, values for 17-ketosteroids and plasma chlorides were reported within normal limits. The basal metabolic rate was within the normal range.

The administration of cortisone was started on Dec. 5, 1949. The first injection was 300 mg. This was followed by administration of 100 mg. daily. By Jan. 17, 1950, the patient had received a total of 3,800 mg. of cortisone; administration was then discontinued. By Dec. 14, 1949, the patient said that she felt improved, with a sensation of mental well-being and improvement of appetite, but she was unable to notice any definite objective physical change as yet. By Dec. 27, 1949, she felt greatly benefited. Complete relief of pain and soreness in and around the involved joints had been obtained. Motion of the shoulders was increased, and she was able to do simple tasks, such as tying her shoes, combing her hair, putting on her coat, and getting dressed, more

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easily and without pain. In addition, she had noted that it took a longer period of exposure to cold to produce the Raynaud phenomenon. However, we were unable to demonstrate any definite objective change in the condition of the skin.

The patient was dismissed on Jan. 24, 1950. She returned on Feb. 6, 1950, with a report that four days after the use of cortisone had been discontinued she had noticed increased aching in the wrists; since that time there had been a gradual increase in disability from stiffness, pain, and aching. There had been no significant change in the Raynaud phenomenon itself. She estimated that her condition had relapsed about 50%. In addition, there had been some loss of appetite and increased tiredness. Additional laboratory examinations at this time disclosed no significant changes in comparison with those done previously. There was no disturbance in the electrolyte balance.

The administration of cortisone was resumed on a dosage of 50 mg. daily on Feb. 9, 1950. After it had been administered for five days there was a lessening of pain and stiffness. On Feb. 15, 1950, she stated that the improvement had become rapid and that it had already progressed to the point which had been attained in two weeks during the first course of cortisone. On Feb. 23, 1950, the dose of cortisone was increased to 100 mg. daily, and additional subjective improvement was noted. The use of cortisone was discontinued on March 11, after 2,000 mg. had been given in this second course. The patient again reported an excellent result subjectively and that she was once again able to do the simple tasks with no more pain, aching, or stiffness; there seemed to be greater flexibility of the skin.

This patient returned again on June 22, after having received testosterone propionate intramuscularly at home. The improvement resulting from the cortisone had been maintained for three weeks after she returned home, but since then relapse had been gradual, until finally the condition which was present before treatment had fully returned. She felt exhausted, and the pains, aches, and stiffness were as severe as previously. She said she had not realized how much she had improved as a result of cortisone until her former condition returned. Clinically, it was felt that there was less tautness of the face and upper part of the chest, but we were unable to demonstrate any change in the skin of the fingers, hands, forearms, and arms. Again, results of laboratory studies were within normal limits. On June 26, 1950, the third course of cortisone was started at the rate of 100 mg. daily for 10 days, for a total dose of 1,000 mg.

In September, 1950, she returned for a fourth course of cortisone. Her condition had remained satisfactory throughout the summer months, but in the previous three weeks there had been a return of her symptoms, although they were not so severe as before.

Case 2.—A white woman, 21 years old, first came to the clinic in August, 1949, with a history of weakness, pain, and limitation of motion of various joints which had begun five years previously, associated with Raynaud's phenomenon. These symptoms gradually progressed. Associated with this progression was a loss of 40 lb. (18 kg.) in the previous three years.

Examination showed Raynaud's phenomenon of the fingers, with tautness of the skin, increased hyperpigmentation of the extremities, particularly the fingers, upper extremities, face, neck, and upper part of the chest. Contractural deformity of the fingers was present. Moderate swelling and tautness of the fingers, hands, and wrists were noted. A diagnosis of "moderately advanced acrosclerosis, with Raynaud's phenomenon" was made. There had been no difficulty in swallowing.

Results of laboratory examinations of the urine, hemoglobin, erythrocytes, and leucocytes, and of a differential blood count were normal. Roentgen examination of the thorax and esophagus disclosed nothing significant. There was little if any widening of the periodontal membranes in roentgenograms of the teeth.

The patient was instructed in physical therapy and was given a prescription of 10 mg. of methyltestosterone to be taken twice daily. She was advised to return in three months for reexamination; this she did, on Nov. 22, 1949. She had obtained no improvement whatever from the previously advised treatment other than mild improvement in appetite. Accordingly, the administration of cortisone was begun on Dec. 9, 1949. On Dec. 14 she said she felt better in general but could name no specific improvement. She felt less stiff, but there was no greater range of motion in the involved joints. By Dec. 20 she felt greatly improved. She had begun to gain weight, there was no further stiffness, and she felt that there was greater mobility in the skin about the face and neck. The edema of the fingers, hands, and wrists had disappeared. There was no change as yet in the skin of the hands. On Jan. 27, 1950, it was found that the

improvement had persisted; there was greater motion in the fingers and less tautness of the skin. The subjective improvement continued. By Jan. 17, 1950, she had received a total of 3,700 mg. of cortisone.

Additional laboratory examinations revealed no essential changes. There was no disturbance of the electrolyte balance. She left our care on Jan. 24, 1950, to return home for two weeks. She returned again on Feb. 6, stating that within a day or two after leaving she had noticed increased stiffness, increased pain, and loss of appetite, but not much change in the skin itself. There was no significant change in Raynaud's phenomenon. On Feb. 10, 1950, the administration of cortisone again was started in a dosage of 50 mg. daily. By Feb. 14 the patient noticed that she was again definitely improved, with less pain and less stiffness. It seemed that the sense of well-being noted previously had returned. She stated that the improvement was now rapid. It progressed to the point that had taken two weeks to reach with the first course of cortisone. This improvement was not maintained, however, and on Feb. 22 the daily dose of cortisone was increased to 100 mg. When this amount was used there were less pain, greater ease of walking and less stiffness, and more rapid improvement. On March 10, 1950, the patient had received a total dose of 1,850 mg. of cortisone.

The patient's local physician was advised that she receive 50 mg. of testosterone propionate intramuscularly twice weekly for eight weeks.

The patient returned on June 15, 1950, stating that three weeks after she had reached her home a post-treatment reaction with marked fatigue had developed and had persisted for a week. Since then, she said, she had done very well, although in May there had been a recurrence of stiffness and pain in the elbows and knees, which was not, however, so marked as she had noticed previously, before she had begun to receive cortisone. Nonetheless, this stiffness gradually had become more marked. There was less hyperpigmentation, the skin was more pliable, and much of the glossiness of the upper part of the chest and fingers was gone. There seemed to be a greater mobility to the face. Laboratory examinations revealed no essential changes and electrolytes were normal.

The third course of cortisone was begun on June 19, 1950, at the rate of 100 mg. daily for 10 days. The patient said she felt much better in general three days later; she reported fewer aches and pains and seemingly less stiffness. The improvement was more rapid than that obtained with the other courses of cortisone.

The patient returned on Aug. 18, 1950, because of increased periarticular pain and stiffness which had recurred shortly after she had gone home in June. The objective cutaneous evidences of scleroderma indicated further regression. The use of cortisone was resumed, 100 mg. being given for 15 days. At the end of this period there was again a practically complete regression of the rheumatoid features of the clinical picture.

CASE 3.—A white woman, 33 years old, registered at the clinic in November, 1949, complaining of swelling of the hands and feet. In December, 1948, after the birth of a second child, she had noticed gradually progressing fatigue. In August, 1949, she had first noticed edema of the hands, face, and feet in association with generalized hyperpigmentation. About this same time she noticed the beginning of Raynaud's phenomenon and difficulty in swallowing.

Examination disclosed generalized hyperpigmentation which was more pronounced on the upper extremities, upper part of the neck, and face, with some edema of the fingers and face and slight tautness and lack of mobility in these areas. She was unable to remain for further investigation but returned on Dec. 9, 1949, for consideration of treatment with cortisone. In the preceding few weeks she had rapidly become worse, with increased shortness of breath, difficulty in swallowing, and increased tautness of the skin of the upper extremities, fingers, and about the face. In addition, there was the first appearance of the ivory glossiness of the upper part of the chest anteriorly.

Results of laboratory examinations, including urinalysis, determination of hemoglobin, erythrocyte and leucocyte count, and differential count, were within normal limits. The sedimentation rate was 60 mm. in one hour (Westergren). Values for urea and sugar in the blood, sodium and potassium in the serum, chlorides in the plasma, 17-ketosteroids and corticosteroids in the urine, and the carbon dioxide-combining power were within normal limits. The result of the flocculation test for syphilis was negative. Roentgenologic examination of the thorax disclosed nothing significant. Roentgenoscopic examination of the esophagus demonstrated scleroderma, with

absence of esophageal peristalsis. Roentgenologic examination showed the stomach to be normal. A diagnosis of "rapidly progressing acrosclerosis with Raynaud's phenomenon" was made.

The administration of cortisone was begun on Dec. 23, 1949, with a dosage of 100 mg. daily. By Dec. 29, the patient said that she felt greatly improved, her skin was less dark, limitation of motion was less, and there was less muscle tenderness. Appetite was improved. The patient no longer was apprehensive or depressed and seemed to be more alert. By Jan. 9, 1950, she had received a total dose of 1,700 mg. of cortisone. The improvement noted previously had been maintained and even increased. In addition, she had gained 3 lb. (1.4 kg.). There was less edema of the hands, but more noticeable edema of the ankles. There was, however, no disturbance in the electrolyte balance. The patient had also noted that it took a longer period of exposure to cold to produce the color changes of Raynaud's phenomenon. Treatment was discontinued on Jan. 24, 1950, after a total of 3 gm. of cortisone had been administered. Results of laboratory examinations at this time, including electrolyte studies, were within normal limits.

The patient was advised to return home for two weeks. She returned to the clinic on Feb. 13, 1950. One week prior to her return she had noticed slight increased stiffness of the knees and increased muscle soreness. However, the skin had continued to be softer and less taut, and she was no longer depressed.

The second course of cortisone was begun on Feb. 17, 1950, at a dosage of 50 mg. daily. Within four days' time she was feeling much improved. She gained weight, and the appearance of a "moonface" was noted. She was now able to walk without pain or stiffness, and motions were still less limited. She completed the second course of cortisone on March 11, 1950, with a total dose of 1,650 mg. She was advised to take testosterone propionate intramuscularly twice weekly at home, in a dose of 50 mg.

The patient returned on April 24, 1950. The improvement obtained from the second course of cortisone had been completely maintained until influenza developed two weeks previously. Since then there had been increased stiffness and pain of the knees and hands, but this had abated spontaneously. The hyperpigmentation was less pronounced, the skin was soft, and the motions and strength appeared good. The "moonface" noted previously, during the second course of cortisone, had disappeared.

The use of cortisone was resumed on April 26, 1950, at a dosage of 100 mg. daily for two days, but then exertional dyspnea appeared and increased. The patient was hospitalized on April 28. Nothing was demonstrated on roentgenologic examination of the thorax or on physical examination. After four days of observation, the patient again began to receive cortisone on May 2, four daily injections of 100 mg. each being given. Shortly after she was dismissed from the hospital on May 5, 1950, a high fever developed, which she felt was a recurrence of the influenza. She was hospitalized again on May 8. In the preceding 48 hours there had developed a dry, nonproductive cough. We were unable to demonstrate objective or localizing signs, but the temperature varied from normal to 104 F. Penicillin was administered intramuscularly. Multiple roentgenograms of the thorax on May 9 and 10 disclosed nothing significant. On May 11 a morbilliform eruption was noted about the patient's face, extending down the trunk. Lesions of the buccal mucosa were suggestive of Koplik's spots; a probable diagnosis of "rubeola (measles)" was made. Aureomycin was administered, but the patient's condition became worse, with signs of encephalitis. The use of aureomycin and penicillin was continued, and fluids were administered intravenously. The patient's course went rapidly downhill. Convulsions developed, the patient became semicomatose, and she died on May 13, 1950. Necropsy revealed only acute extensive bronchopneumonia as a cause of death. No micro-organisms could be produced by culture of specimens of tissue obtained at necropsy.

CASE 4.—A white woman, 36 years old, first came under our care in 1948 because of scleroderma with calcinosis of five years' duration. She had been hospitalized, during which time she had received various types of therapy, including the use of fever, papaverine, vitamin K, physical therapy, and bismuth given intramuscularly. She had then returned home, feeling improved but without demonstrable objective change.

Because of increase of the calcinosis and development of secondary infection in certain of the involved areas, the patient returned to the clinic on Feb. 20, 1950. There had been no progression of the scleroderma. Raynaud's phenomenon had disappeared in 1949. Because of the increase in calcinosis, however, the patient necessarily had remained bedridden for the previous 10 months.

Examination disclosed generalized scleroderma, with generalized hyperpigmentation and marked contracture deformity of the fingers. In addition, there were superficial and deep calcific nodules about the elbows, knees, and thighs and overlying the sacrum and iliac bones. Results of laboratory examinations were noncontributory except for the characteristic periodontal widening seen in the dental roentgenogram of patients who have scleroderma, the roentgenologic demonstration of calcium in the previously noted areas, a sedimentation rate of 115 mm. in one hour (Westergren), and increased protein and globulin values (9.0 and 5.1 gm., respectively).

Physical therapy in the form of mild heat, massage, and passive and active motion was begun, followed on Feb. 25, 1950, by surgical excision of the large deposits of calcium overlying the sacrum and about the left knee and elbow. Penicillin was given intramuscularly during the patient's convalescence to prevent secondary infection. The surgical incisions healed without incident. Additional deposits were excised from the right and left trochanteric areas and right elbow on March 11. The patient was more comfortable as a result of removal of the calcium, but otherwise no change was noted, either subjectively or objectively.

The use of cortisone was begun on March 20, 1950. The agent was administered intramuscularly in doses of 100 mg. daily for 14 days. On the fifth day the patient said the aching and pain about the joints had diminished; on the seventh day she said that she felt fine in every respect. The skin seemed softer and more mobile. The patient began to try to walk again. Appetite increased, and the euphoria described by other patients apparently was present. The administration of cortisone was discontinued on April 1, but improvement, both subjective and objective, continued until the patient was dismissed on April 18.

During and after the administration of cortisone the laboratory findings changed but little: The sedimentation rate decreased from 115 to 100 mm., the values for proteins varied from 9 to 7.37 gm. per 100 cc. of serum and for globulin, from 5.1 to 3.76 gm. per 100 cc. of serum, findings considered of doubtful significance. No change could be demonstrated roentgenologically in the amount of calcium present in the tissues before and after therapy.

Correspondence from the patient in May, July, and September, 1950, indicated that pain had continued to abate and that there was improvement in the patient's ability to walk and to perform simple tasks. She said there had been no further deposition of calcium, to her knowledge.

COMMENT

Scleroderma or acrosclerosis is a disease for which there is neither a specific treatment nor a known cause, one which is disabling, mutilating, and painful, and one which may produce death. Heretofore the treatment has consisted of physical therapy, the use of vasodilating agents of various types, neostigmine, testosterone, and other even less effective agents. To certain patients who previously had been treated with other methods or agents, cortisone afforded much more benefit. They all felt greatly improved, particularly in the sense of general well-being, appetite, strength, and ability to perform simple tasks (combing hair, dressing, tying shoelaces, and walking upstairs). Pain, soreness, and discomfort greatly diminished or ceased. The rapidity and magnitude of this improvement, particularly in respect to the symptoms and manifestations simulating those of rheumatoid arthritis, are far greater than we have been able to achieve with other methods of treatment.

The beneficial effects do not appear to be lasting; all symptoms reappear at varying lengths of time after completion of a course of treatment. Resumption of treatment, however, appears to bring about the same improvement in less time and with a smaller total dose than had been required in the preceding courses of therapy. It may be that a gradual decrease of doses and then an endeavor to find a low maintenance dose will provide more lasting benefits. Cortisone cannot be administered in moderate or high doses for long periods without the potentiality of development of untoward reactions.

The sense of well-being to the point of euphoria was noted in all patients treated. We cannot but think that some of the increased ability to perform simple tasks and

other symptomatic improvement may be due in part to this sensation. As indicated elsewhere,[1] we have been unable to demonstrate significant increased peripheral circulation or increased skin temperatures in patients with scleroderma treated with cortisone or corticotropin (ACTH). Other objective evidences of improvement were manifest, although not pronounced. The skin became softer and less taut, there was greater mobility of the skin, especially about the face and hands, the joints were more mobile, and in heavily hyperpigmented patients there was a partial disappearance of the excess pigment.

Specimens of skin for microscopic examination were removed from contiguous sites from three of the four patients (Cases 1, 2, and 3) before, during, and after treatment. Even at the end of the total treatment period, and after repeated courses of therapy, we were able to demonstrate histologic improvement in only one patient (Case 2).

The death of the patient concerning whom the clinical findings of measles and encephalitis were made, and necropsy findings of acute extensive bronchopneumonia were reported, again points to repeated statements of others that cortisone should not be administered to those who have acute infection. The acute symptoms leading to the death of this patient first appeared 24 hours after the use of cortisone had been discontinued. A total dose of 700 mg. had been given.

Corticotropin was administered to two additional women who had acrosclerosis. One received 80 mg. once daily for 10 days with no beneficial response whatever in an observation period totaling 33 days. The other patient received 75 mg. daily (25 mg. at 10 a. m. and 50 mg. at 4 p. m.) for a total dose of 1,200 mg. In this patient, similarly, there was no demonstrable objective or subjective improvement in six weeks' time after therapy. The lack of improvement from the use of corticotropin may be due to insufficient doses and to too-infrequent administration. More patients must be treated and observed before it will be possible to determine the therapeutic efficiency of corticotropin in relation to that of cortisone.

SUMMARY AND CONCLUSIONS

Four patients who had scleroderma have been treated with one or more courses of cortisone. All patients exhibited marked improvement, especially in the rheumatoid manifestations, during and shortly after the treatment. In three patients the symptoms reappeared within a few weeks after treatment had been discontinued, whereas in the fourth patient the remission was maintained for at least five months after treatment.

Treatment was repeated for three patients; in these the same degree of improvement appeared in less time and with a smaller total dose than had been required in the first course.

Corticotropin (ACTH) has not been effective in the treatment of two patients with scleroderma. This may be due to improper timing of the administration.

Cortisone provides the most pronounced clinical benefit of any agent yet used in the treatment of scleroderma, producing definite remissions of symptoms of varying duration; yet it does not cure the scleroderma.

1. Hines, E. A., Jr.; Wakim, K. G.; Roth, G. M., and Kierland, R. R.: The Effect of Cortisone and Adrenocorticotrophic Hormone (ACTH) on the Peripheral Circulation and Blood Pressure in Scleroderma; abstracted, J. Lab. & Clin. Med. **36**:834 (Nov.) 1950.

PHYSIOLOGICAL AND CHEMICAL CHANGES IN RADIATION INJURIES

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WITHIN the past few years so many important contributions have been made in the field of radiation physiology that one need hardly apologize for the sketchiness of any short paper intended to summarize the state of affairs. In the discussion which follows there are sure to be regrettable omissions and instances of misplaced emphasis.

Fortunately, in addition to the hundreds of papers reporting original research work, there have been some excellent reviews. Especially easy of access is the chapter on the physiological effects of radiant energy by Shields Warren [1] in the *Annual Reviews of Physiology* for 1945, which gives an excellent idea of the state of our information in that year. There is a comparable article in the *Annual Reviews of Physiology* for 1950 by Abraham Edelmann.[2] These two reviews have been invaluable in the preparation of this paper. Both afford keys not only to original reports but also to other reviews and tabulations.

Among available books, there are several that have seemed especially worthy of attention:

1. An especially clear presentation of the subject of nuclear radiation physics is given in a book under that title by Lapp and Andrews.[3] Attention is called to the text and diagrams (pp. 80 to 88) relating to the photoelectric effect, Compton effect, and pair production, which are to be mentioned below.

2. For a general discussion of ionizing radiations, a good summary of the problem of dosage, and an introduction to the subject of biological reactions to such radiations, a useful book is "Physical Foundations of Radiology" by Glasser, Quimby, Taylor, and Weatherwax.[4]

3. A remarkably clear and compact recent summary in German is "Röntgen- und Radiumphysik" by Glocker.[5]

4. The therapeutic possibilities of higher-voltage roentgen rays are discussed in a new book "Supervoltage Roentgentherapy" by Buschke, Cantril, and Parker.[6]

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1. Warren, S.: Ann. Rev. Physiol. **7**:61-74, 1945.

2. Edelmann, A.: Ann. Rev. Physiol. **12**:27-46, 1950.

3. Lapp, R. R., and Andrews, H. L.: Nuclear Radiation Physics, New York, Prentice-Hall, Inc., 1948.

4. Glasser, O.; Quimby, E. H.; Taylor, L. S., and Weatherwax, J. L.: Physical Foundations of Radiology, New York, Paul B. Hoeber, Inc., 1944.

5. Glocker, R.: Röntgen- und Radiumphysik, Leipzig, Georg Thieme, 1949.

6. Buschke, F.; Cantril, S. T., and Parker, H. M.: Supervoltage Roentgentherapy, Springfield, Ill., Charles C Thomas, Publisher, 1950.

5. A recent contribution to the history of ionizing radiations is the book, "X-Ray Treatment: Its Origin, Birth, and Early History" by Grubbé.[7] It describes, among other things, a consultation held in January, 1896, over the severe dermatitis in his left hand after overexposure to roentgen rays.

6. A book that deserves to be reread occasionally and to be called to the attention of every student of ionizing radiations is "American Martyrs to Science Through the Roentgen Rays" by Percy Brown.[8]

7. The book, "Histopathology of Irradiation from External and Internal Sources," edited by William Bloom,[9] is one of a series of about 60 volumes which are expected to constitute the National Nuclear Energy Series. It has 808 pages and is a detailed, thoroughly illustrated report on extensive animal experiments with all kinds of ionizing radiations.

IONIZATION

The radiations with which this paper is concerned are the alpha, beta, and gamma radiations from radium (and from other naturally or artificially radiative elements), roentgen rays, grenz rays, the ultraviolet radiations of shorter wave lengths, and neutron beams. All of them have one property in common, namely, that when these radiations pass through air they fill it so full of conducting particles that its electrical resistance falls markedly. The conduction of current is due to the movement of many small particles carrying charges, and they are called ions. It is therefore convenient to refer to all of these radiations simply as "ionizing radiations."

Now, it is an important fact that these radiations are similar not only physically but also physiologically. That is one of the most significant conclusions from recent work. It has been established finally by the reports from the Manhattan Project by Bloom and his colleagues. Only in the case of the bone marrow of the metaphysis did they find even a suggestion of qualitative difference between roentgen rays and other ionizing radiations.[10] In all other instances they found "no qualitative differences in the reaction of animals to comparably effective doses of x-rays, gamma rays, fast and slow neutrons, and (for the skin) external beta rays." If these rays are administered in doses that will kill half the animals in 30 days, their histologic effects on any given animal species cannot be told apart.

This principle could not be assumed to hold until it was established by actual experiment, especially because the radiations concerned are at first sight so different. The alpha particle, for instance, is a relatively ponderous object with a strong charge; the neutron is also relatively heavy, but with no charge at all; and the gamma ray is not a particle but an undulation. Two facts, however, account for the similarity of their effects. One is the fact emphasized by the work of de Broglie that these radiations all have a sort of double nature, and consequently the rapidly moving particle can at times be conveniently represented, at least by the mathe-

7. Grubbé, E. H.: X-Ray Treatment: Its Origin, Birth, and Early History, St. Paul, Bruce Publishing Company, 1949.

8. Brown, P.: American Martyrs to Science Through the Roentgen Rays, Springfield, Ill., Charles C Thomas, Publisher, 1936.

9. Bloom, W.: Histopathology of Irradiation from External and Internal Sources, New York, McGraw-Hill Book Company, Inc., 1948.

10. Bloom,[9] p. 748.

matician in his equations, as an undulation of a frequency related to the energy of the particle, while the undulatory radiation, on the other hand, comes off in quanta that are indivisible, as if they were elementary particles.

The other fact is that the absorption of a quantum of an undulatory radiation, such as the roentgen ray, actually is followed by the emission of a particle, namely the electron. The incidence of a quantum of roentgen ray (a photon of high energy content compared with that of visible light) is likely to be followed by one of three possible events: (1) photoelectric effect, (2) Compton effect, or (3) pair production. In the photoelectric effect, a photon enters the atom; out comes an electron. We now have two particles, the moving electron with its negative charge, and the rest of the atom left with a positive charge. Thus there has been ionization. Naturally the electron can go on and produce secondary ionization by further collisions. In the Compton effect, a photon enters the atom; out comes a photon of less energy, together with an electron. In pair production, a photon enters the atom; out comes a pair of particles, one an ordinary electron (negatron), the other a positive electron (positron). Pair production is of great theoretical interest because it illustrates the conversion of energy into matter.

The photon may, of course, miss any given atom. If it goes through a structure without a single hit, there has been no absorption, and so there is no effect. The relative likelihood of the three possibilities described depends on the energy of the incident photon. This is well shown by a diagram given by Lapp and Andrews on total absorption in lead. The more energetic photons (that is, gamma rays and supervoltage roentgen rays) yield more pairs per collision than do low-voltage roentgen rays.

EFFECTS ON WATER

Just what happens after a photon of gamma-ray or roentgen-ray energy has hit an atom within a living organism has long been uncertain. An attractive idea was the hypothesis that the ionization known to be produced resulted in the upsetting of enzyme systems, but the early experiments were negative. The history of this work is sketched by Barron, Dickman, Muntz, and Singer.[11] The early experiments were done with concentrated solutions of enzymes, on the supposition that the more densely crowded the enzyme molecules, the more likely they were to be hit by the photons. The work by Barron and his associates shows that this idea was wrong, and that the more dilute the enzyme solution, the stronger the effect of irradiation. This is borne out by experiments with many kinds of enzymes. Whereas the earlier workers found concentrated enzyme solutions resistant to enormous doses of roentgen rays (above 5,000), dilute solutions are very sensitive.

It is supposed, then, that a photon of roentgen or gamma radiation, on striking a water molecule, liberates a fast-moving electron from one of the atoms, and that this is followed by the appearance of many different short-lived radicals, such as H_2O^-, H_2O^+, OH, H, HO_2, O, and H_2O_2. Thus the effect is primarily on the water, and secondarily there is the inactivation of the enzyme.[12] This is quite

11. Barron, E. S. G.; Dickman, S.; Muntz, J. A., and Singer, T. P.: J. Gen. Physiol. **32**:537-552, 1949.

12. The report of Barron and his associates [11] is summarized by Edelmann,[2] p. 30.

in harmony with what is known about the complex nature of liquid water (to say nothing of at least five kinds of ice known to be possible in solid water), and the probable existence of $(H_2O)_2$, $(H_2O)_3$, and H_3O. Mazia and Blumenthal [13] showed that a large number of enzyme molecules in a film may be affected by the spread of a single ionization, and Krenz [14] found evidence for the prolonged existence of "excited polymers" in irradiated water.

The result of this is that a single hit can kill a whole cell. This phenomenon was observed by Lorenz and Henshaw [15] in a marine vibrio, Achromobacter, and by Henshaw and Turkowitz [16] in a yeast. In the case of the yeast, some of the cells "lethally affected did not die immediately but underwent several subdivisions following exposure before disintegration."

The effect of dilution observed by Barron in enzymes in vitro explains the finding by Wertz [17] that barley grains are the more sensitive to radiation the greater their water content. This may have some relation to another fact emphasized by Failla [18]: The swelling of cells and cell nuclei is important. Anything that favors the imbibition of water by the cell or its nucleus enhances the lethal effect of the radiation. "Wolf noted that marked vacuolization in tumor cell cytoplasm and in nuclei may persist for as long as five months after the cessation of radiation."[19]

Barron suspects that the effect of the ionization is to oxidize the sulfhydryl (-SH) groups of such enzymes as phosphoglycerylaldehyde dehydrogenase, adenosinetriphosphatase, and succinoxidase. There is a reversible stage during which the addition of glutathione will reactivate the enzyme. Beyond this there is an irreversible stage in which glutathione no longer avails. This is the stage of denaturation, and can be produced in enzymes, such as trypsin, catalase, and ribonuclease, which do not have -SH groups. Such inactivations have been obtained by using roentgen, alpha, beta, and gamma rays. All four radiations are alike in this respect.

RADIOSENSITIVITY AND RADIORESISTANCE

The preceding discussion brings one naturally to another important subject, that of radioresistance and radiosensitiveness. The differences in sensitiveness between species, between the old and young within a given species, and between the tissues within a given individual are astonishing, because they amount to several orders of magnitude. For instance, Halberstaedter and Back [20] found that 300,000 to 600,000 r were needed to kill the alga Pandorina immediately. The protozoan Paramecium required 200,000 to 700,000 r. Brain cells of goldfish are affected by 100,000 r, according to Ellinger.[21] These species are quite different from the guinea pig, for instance, for which the fatal dose is less by three orders of magnitude. A

13. Mazia, D., and Blumenthal, G., cited by Edelmann,[2] p. 31.
14. Krenz, F. H., cited by Edelmann,[2] p. 31.
15. Lorenz, K. P., and Henshaw, P. S., cited by Warren,[1] p. 63.
16. Henshaw, P. S., and Turkowitz, H., cited by Warren,[1] p. 63.
17. Wertz, cited by Warren,[1] p. 64.
18. Failla, G., cited by Warren,[1] p. 66.
19. Wolf, K., cited by Warren,[1] p. 66.
20. Halberstaedter, L., and Back, A., cited by Warren,[1] p. 64.
21. Ellinger, F., cited by Warren,[1] p. 71.

single exposure of 175 r given to 100 guinea pigs results in the death of half of them in 30 days, i. e., the medial lethal 30-day dose is 175 r. For the rat the corresponding figure is 600 r.[2]

Within the rat, the difference among tissues is surprising. Goldfeder [22] found that rat kidney growing in vitro was extremely resistant to radiation, for 300,000 r applied for 30 minutes failed to alter either oxygen uptake or aerobic glycolysis. This is in agreement with the results reported by Bloom.[23]

In contrast to resistant organs, such as the kidney, liver, and lung, it is well known that the testes are radiosensitive. But within these organs there are marked differences among the cell types. Bloom found that the spermatogonium was the most radiosensitive of the spermatogenic cells, and that when damage in animals receiving internal radiation was severe enough there was gradual elimination of spermatogonia, spermatocytes, spermatids, and spermia, until only apparently unchanged Sertoli cells were left. The interstitial cells were extremely radioresistant.[24]

While the liver is resistant to the direct action of iodizing radiations, it may show cell damage and atrophy when an animal is killed, for instance, after injections of small amounts of plutonium.[25] This finding is corroborated by Rhoades,[26] but she is inclined to believe that the effects on the liver are secondary reactions due to toxicity or arising from some cause extraneous to irradiation.

Warren and Dixon [27] found that the testes and ovaries of chick embryos and young chicks continuously irradiated by means of injections of phosphorus 32 were the most radiosensitive structures and the least able to recover from injury. The primitive sex cells were the most sensitive, the spermatogenic cells were sensitive all throughout development while the ova became more radioresistant as they matured.

Details about the many complicated effects of radiations on the ovary and related endocrine organs are given by Edelmann [2] but will not be recounted here.

CONTROL OF RADIOSENSITIVITY

While many of the factors that determine radiosensitivity are unalterable, there must be many that are subject to control.

1. The degree of dehydration of an organism should be important, but in man, unfortunately, it cannot be made to vary within very wide limits. In animals attempts have been made to control the degree of hydration by controlling the dietary intake of water and salts. This was done, for instance, by France.[28] He found that animals dehydrated by dietary water restriction lived longer than controls.

2. A considerable list of substances have been studied to see whether they would counteract the well-known tendency to hemorrhage that follows irradiation. The following are mentioned by Edelmann [29]: flavonoid substance from lemons, rutin,

22. Goldfeder, cited by Warren,[1] p. 72.
23. Bloom,[9] p. 682.
24. Bloom,[9] p. 569.
25. Brues, A. M., cited by Edelmann,[2] p. 38.
26. Rhoades, cited by Bloom,[9] p. 541.
27. Warren, S., and Dixon, F. I., cited by Edelmann,[2] p. 36.
28. France, O., cited by Edelmann,[2] p. 37.
29. Edelmann,[2] p. 34.

hesperidin, epimerized d-catechin, hesperidin methyl chalcone, esculin, quercitrin, naringin, semicarbazone of adrenochrome, pyridoxine, and folic acid. There is much disagreement in regard to these substances, especially rutin.

3. There has been debate as to the possibility that histamine might be important in producing some of the symptoms of radiation sickness. On this assumption, desoxycorticosterone has been tried. Positive results have been reported. It has also been reported that antihistaminics applied to the skin as ointments are beneficial in cutaneous reactions to radiation. However, a potent antihistaminic tried by Brown and Hunter was found to be without value in the treatment of radiation sickness.

4. Patients with nausea and vomiting due to radiation sickness have been reported to exhibit low niacin and riboflavin excretions. They were reported to benefit from treatment with B-complex vitamins.[30] The reviewer does not state whether the psychic element was properly controlled in this study, and whether the possibility of centripetal drift in the laboratory data was considered.

5. An investigator reported that desoxycorticosterone protected the liver against fatty changes caused by irradiation. In view of the uncertainty as to the cause of liver damage after irradiation, the meaning of this result is debatable.

These results do not seem especially encouraging, but this line of experimentation will have to be followed much further, for in it seems to lie the hope of increasing resistance to threatened radiation injury and of improving the irradiation treatment of neoplastic disease. The study of these factors seems more promising, for instance, than would be the further exploration of supervoltage roentgen rays.

The latter subject is discussed in the recent book by Buschke, Cantril, and Parker which was mentioned in the beginning. After a thorough experimental study of this subject, they reach the following conclusion[31]: It "is theoretically unlikely . . . that a further increase in voltage of x-rays will add appreciably to curability of cancer by increase of depth dosage alone." Likewise, after considering the relative effects of irradiation upon neoplastic tissue and upon the regenerative processes necessary for wound-healing, they explain why they omit "postoperative radiation after a carefully done operation" in carcinoma of the breast. All of these facts argue strongly in favor of more extensive study of the reasons for differences in radiosensitiveness of tissues under various conditions.

ALLEGED STIMULATION BY IONIZING RADIATIONS

The older literature of roentgenology used to furnish examples of the phrase "stimulating doses of x-rays." It was possible for this idea to persist as long as nobody actually measured the activity of an organ so as to get actual evidence of increased activity after irradiation. The idea was disposed of when Ivy, Orndoff, Jacoby, and Whitlow[32] actually measured the amount of secretion produced by certain gastrointestinal glands and showed that irradiation never increased production, but only decreased it. Recent observations have amplified this finding. Reduction in the intestinal stroma was reported by Ely and Ross,[33] and Ricketts

30. Edelmann,[2] p. 38.

31. Buschke, Cantril, and Parker,[6] p. 290.

32. Ivy, A. C., and others: J. Radiol. **4**:189-199, 1923.

33. Ely, J. O., and Ross, M. H., cited by Edelmann,[2] p. 38.

and his associates found hyperemia, hemorrhage, edema, and atrophy in the gastric mucosa after roentgen irradiation. Measurements of tensile strength of wounds [34] showed interference with healing.

Irradiation is supposed to be beneficial in some infections. If it is, the effect is not attributable to the killing of bacteria, since they are generally very much more resistant to radiation than are human cells. Neither does irradiation cause any striking increase in the effectiveness of the body's immunological defense mechanisms. The subject of benefits ascribed to irradiation in various infections is broad, and has been reviewed by Pendergrass and Hodes.[35]

A distinction must be made between the hyperemia which is seen immediately after the application of heat to a part and the erythema which develops hours or days after application of ionizing radiations to the skin. While the former, the hyperemia, is an active functional state generally conceded to be helpful in overcoming infections, it is now believed that the erythema is an anatomical change involving a reduction of the elastic components of the perivascular tissue and a weakening of the walls of the vessels themselves. The erythema is a persistent, unphysiological state, and seems unlikely to prove beneficial in overcoming infections. The introduction of the bat as a laboratory animal will undoubtedly yield valuable new information on this point, for the bat's wing is so thin and transparent that the capillaries can be observed under good magnification, time after time, without disturbing their normal functions either by anesthetics or by surgery. It would seem to be ideal for the study of the effect of ionizing radiations on mammalian blood vessels. The depressing, destructive effects of ionizing radiations on the blood, the blood-forming organs, and the lymphoid tissues are extensive, but they are so well known that they will not receive further notice in this paper.

SUMMARY AND CONCLUSIONS

It has not been possible to suggest more than a few of the important problems related to the biological effects of ionizing radiations. One of the most difficult problems, which has not been mentioned, is that of dosimetry and the equivalence of physical and physiological units of radiation. Connected with it is another problem of more recent origin, namely, how many neutron units are equal to one roentgen unit, how many "n" equal one r. The following statements, however, summarize the most important points of the paper:

1. Alpha, beta, and gamma rays, roentgen rays, shorter ultraviolet wave lengths, and neutron beams all act by causing the discharge of free electrons from atoms; this causes chemical changes in water, upsets enzyme systems, depresses functions, and destroys cells. These rays can, therefore, all be referred to as ionizing radiations.

2. They stimulate rarely, if ever. Their action is primarily depressing and destructive.

3. The wide ranges of radioresistance observed in various test objects under varying conditions may afford clues leading to better control of their biological effects.

535 N. Dearborn St. (10).

34. Warren,[1] p. 69.

35. Pendergrass, E. P., and Hodes, P. J., cited by Edelmann,[2] p. 63.

PROGESTERONE THERAPY OF ACNE

A Clinical Evaluation

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THERE is now little doubt that sex hormones play an important role in the production and perpetuation of acne vulgaris. Sufficient data have accumulated to indicate that an increase of the androgen-estrogen ratio is found in many acne patients. However, therapy designed to regulate this hormonal imbalance has, for the most part, produced ambiguous results, and studies continue to appear in the dermatologic literature which indicate that the search for the "ideal" hormonal therapy goes on.

Way and Andrews [1] stated, "The statistics obtained in our series clearly demonstrate the value of sex hormones in the treatment of acne vulgaris, and their use seems justifiable when satisfactory results are unobtainable by commoner methods of therapy." In their study, three series of patients were followed. Of the various hormones administered, the authors obtained best results by the subcutaneous administration of progesterone. Of 20 patients who received progesterone therapy alone, 75% had suffered premenstrual exacerbations and 30% had noted irregular menses prior to therapy. A hormonal imbalance was considered present in 75%, questionable in 10% and lacking in 15%. In this group of patients, results were good in 45%, fair in 30%, and poor in 25%.

When one considers that previous therapy in most of these patients had produced either temporary, doubtful, or no response, the percentage of improvement appeared quite significant and worthy of corroboration.

METHOD

We employed a preparation containing 20 mg. per cubic centimeter of progesterone in propylene glycol with 4% ethyl aminobenzoate (benzocaine).[2] A dose of 0.3 cc. of this preparation (6.6 mg. of progesterone) was administered subcutaneously at weekly intervals. Adjunctive therapy during this study was limited to dietary restrictive measures and topical applications, which prior to progesterone therapy had not materially affected the course of the disorder.

1. Way, S. C., and Andrews, G. C.: Hormones and Acne: A Clinical Evaluation of Hormonal Therapy in Adolescent Girls with Acne, Arch. Dermat. & Syph. **61**:575 (April) 1950.

2. Ciba Pharmaceutical Products, Inc., Summit, N. J., supplied the hormone preparation used in this study.

Effect of 6.6 Mg. of Progesterone Administered Subcutaneously at Weekly Intervals on Twelve Patients with Therapy-Resistant Acne

Patient	Sex	Age, Yr.	Duration, Yr.	Previous X-Ray Treatment	Premenstrual Exacerbation	Irregular Menses	Total Injections	Results				Comment
								Excellent	Good	Equivocal	Poor	
L. M.	F	19	10	+	0	0	9	..	..	..	+	.....
P. M.	F	18	3	+	++	0	9	..	..	..	+	.....
H. B.	F	28	10	+	+	0	10	..	..	+	..	.....
J. A.	F	23	7	+	+++	++	6	..	..	..	+	.....
L. M.	F	27	14	0	++	+	6	..	..	..	+	Dysmenorrhea relieved
A. A.	F	17	4	0	++	+	5	..	+	..	..	Dysmenorrhea relieved; concomitant x-ray treatment
C. H.	F	19	6	+	+++	0	6	..	..	..	+	.....
E. A.	F	24	7	+	+++	0	7	..	..	+	..	.....
P. C.	F	16	½	0	++++	+	4	..	..	+	..	.....
D. J.	F	26	10	+	+	0	4	..	..	+	..	.....
R. W.	M	21	6	+	?	?	7	..	..	..	+	.....
R. L.	M	19	1½	0	?	?	12	+	..	..	..	Almost clear of severe acne

SELECTION OF PATIENTS

No attempt was made to employ progesterone for the "average" or usual acne patient. In general, only those patients who had not responded to ordinary therapeutic measures were included in this study. Most patients had already received a full course of x-ray therapy, either in this office or elsewhere, with either temporary or unsatisfactory results.

We felt that the progesterone effect could be scientifically evaluated in 12 patients. Ten other patients received progesterone therapy, but a lack of prompt response necessitated adjunctive or alternative measures, thereby vitiating adequate experimental data. Of the female patients, 90% had noted premenstrual exacerbations; irregular menses and/or significant dysmenorrhea were present in 40% prior to treatment.

RESULTS

Of the 12 patients treated, response was good in one, excellent in one, equivocal in four, and altogether lacking in six. Those patients in whom response was considered "equivocal" felt that they had achieved improvement, but no objective evidence of diminished activity was noticeable clinically. In the group labeled "poor" there was no indication of either subjective or objective improvement. The accompanying table is largely self-explanatory.

Our one excellent result was obtained in a white youth (R. L.) in whom a severe, conglobate acne of the face, chest, and back had developed over a period of 18 months despite dietary restriction, administration of foreign protein, short-wave ultraviolet irradiation, and topical therapy. His family was opposed to the use of roentgen irradiation. Improvement was observed clinically after three injections of progesterone at weekly intervals and continued to almost-complete clearing after 12 injections.

A white girl (A. A.) had had severe papulopustular facial acne for four years. Although we feel that her marked improvement was due to concomitant x-ray therapy, it is noteworthy that her severe dysmenorrhea, present at the onset of each prior menses, was not evident in the two menstrual periods during the course of progesterone therapy. She is included in the series for this reason only.

COMMENT

In general, our results were disappointing. In only one case could well-defined improvement be considered attributable to progesterone. In all others, there was no significant objective therapeutic response, although dysmenorrhea was relieved in two patients. Perhaps continuation of progesterone injections might have produced better results. However, when no improvement was noted after several weekly injections, patients became discouraged and wished to discontinue this form of therapy. It is possible that our rigid selection of therapeutically nonresponsive patients accounts for the poor results obtained.

SUMMARY

A clinical study of 12 patients with acne resistant to ordinary therapy is reported. All patients received 6.6 mg. of progesterone subcutaneously at weekly intervals. One male patient responded well to 12 such injections. Improvement attributable to progesterone was negligible in the remainder under the conditions of this study.

2200 E. Eighteenth Ave. (6).

EVALUATION OF CHLORAMPHENICOL IN THE TREATMENT OF CHRONIC DISCOID LUPUS ERYTHEMATOSUS

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IN JUNE, 1947, chloramphenicol [1] was first given to a patient with chronic discoid lupus erythematosus. All of the other currently advocated drugs (gold sodium thiosulfate, bismuth by mouth and by intramuscular injection, and para-aminobenzoic acid) had given such uniformly poor results that this antibiotic drug was tried in the hope that it might prove of greater value than the others.

The improvement in the lesions in the first patient treated was so noticeable and rapid (within one week) that it was decided to continue the treatment for this patient, and 12 more patients with the same disease were added, making a group of 13 under treatment. Patients were given 1 or 1.25 gm. of chloramphenicol divided into four or five doses of 250 mg. each.

The results at that time seemed of sufficient academic interest to warrant a preliminary report.[2] All of these patients have now been followed for about one and one-half years, and developments have occurred that make a further report desirable.

In addition to the original 13 patients, three more have been included. Only one patient had a change in treatment routine, and that one received combined oral and intravenous chloramphenicol therapy. Because of the local irritant reaction on the veins, the intravenous injections were discontinued after the fourth one.

For purposes of easier handling, these patients have been divided into five groups.

GROUP 1

One patient in whom there was no visible effect comprises Group 1.

CASE 1.—A. C., a 63-yr.-old, married Negro woman, was first seen in April, 1947, presenting numerous lesions on the scalp, face, and ears, all showing old atrophic scars but with active hyperpigmented margins with follicular plugging. The condition began in 1936. She had received 12 intramuscular injections of bismuth subsalicylate between April and August, 1947, without improvement.

She returned to the clinic in July, 1949. Results of urinalysis were normal, and serologic tests for syphilis elicited negative reactions. Oral chloramphenicol therapy was begun, and she was given one 250-mg. capsule four times a day. After the first week she claimed that she "felt better," but there was no objective improvement, and after she had taken 238 capsules,

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From the Department of Dermatology, School of Medicine, University of Maryland.

1. E. A. Sharp and Parke, Davis & Company assisted in this study by supplying the chloromycetin.®

2. Robinson, H. M.: Chloramphenicol (Chloromycetin) in the Treatment of Chronic Discoid Lupus Erythematosus: A Preliminary Report, J. Invest. Dermat. **14**:309 (May) 1950.

this treatment was discontinued in October, 1949. In October, 1950, she was again given intramuscular injections of bismuth subsalicylate once a week for six weeks; treatment was again stopped, no improvement having been obtained.

GROUP 2

Group 2 includes six patients in whom all lesions regressed, and who are at present free of lesions.

CASE 2.—M. T., a married Negro woman, 26 yr. old, was first seen in June, 1949. There were five lesions on the left cheek, the first of these lesions having appeared two years before the initial visit. She had received no previous medication. Examination revealed the urine to be normal, and reaction for serologic tests were negative for syphilis. Oral chloramphenicol

Fig. 1.—(Left), E. A. (Case 3), chronic discoid lupus erythematosus of four-years-and-three-months' duration and exacerbation of five-days' duration. (Right), E. A., after administration of 252 capsules of chloramphenicol.

(chloromycetin®) treatment was begun, with a dosage of one capsule four times a day. Treatment was discontinued on Oct. 15, 1949, all lesions having involuted. She was asked to return should the lesions recur. Lesions did not recur, but she returned Nov. 19, asking for more treatment for fear that the lesions would recur. She was again discharged in March, 1950, and her condition has remained clear. She had taken 700 capsules in all.

CASE 3.—E. A. (Fig. 1), a 25-yr.-old white married woman, was first seen in September, 1945. She had already received elsewhere 12 injections of gold sodium thiosulfate and five intramuscular injections of bismuth. Bismuth sodium triglycollamate ("bistrimate") tablets were prescribed, which she took for eight months. None of this therapy had produced any effect on the lesions.

Results of urine examination were normal, and the reaction to a serologic test was negative for syphilis. Chloramphenicol therapy was begun in August, 1949, 1 gm. a day, and she was

discharged in October, 1949, as completely cleared, having taken 252 capsules. In August, 1950, she returned with a recurrence of one lesion, which cleared up after she had taken 28 capsules. To date the condition has remained clear.

CASE 4.—M. R., a 42-yr.-old married Negro woman, had two lesions for two years, but had received no treatment. Chloramphenicol therapy was started on Aug. 4, 1949. Although there was immediate improvement after the first week of treatment, she was very irregular in her visits, of which she made 23 from Aug. 4, 1949, to June 8, 1950. She was provisionally discharged on the latter date, as both lesions had completely regressed. She had taken 672 capsules.

CASE 5.—D. M., a 41-yr.-old married Negro woman, was first seen in August, 1949, presenting about 20 lesions on her face and chest, which had been present for five months. Her only treatment had been ointments. She was given chloramphenicol treatment, receiving 1 gm. a day. On Jan. 23, 1950, some improvement was noted. From this date, continuous improvement was seen. She was provisionally discharged June 26, 1950, as "cured," having received 952 capsules.

CASE 6.—G. R., a 35-yr.-old married white woman, was first seen Sept. 6, 1949, with several lesions on the vermilion border of the upper lip, the largest of which measured 1 by 1.5 mm. After diagnosis, the patient was given chloramphenicol, 250 mg. every four hours. On Sept. 26, all but one lesion had regressed. On June 12, 1950, the patient was discharged, all lesions having involuted after she had taken 560 capsules.

CASE 7.—A. P., a 27-yr.-old white married woman, was admitted in April, 1948. Elsewhere she had already received five intramuscular injections of bismuth, five intravenous injections of gold sodium thiosulfate, and five x-ray treatments.

At the time of her admission she was given bismuth sodium triglycollamate tablets, two or three times a day. After weeks of this treatment without any results, she was given, on June 3, 1948, carbarsone tablets, one the first day, two the second day, and three a day thereafter. On Nov. 6 there was only one small active lesion remaining. On Sept. 20, 1949, she returned with a recurrence of four lesions on her face, the largest 1 cm. in diameter, and four in her scalp, the largest 2.5 cm. in diameter. She was given chloramphenicol treatment, one 250-mg. capsule four times a day. On Sept. 30, 10 days later, I noted that the lesions were constantly improving. She complained that she had nausea when she took the capsules around meal time. Because of the nausea the treatment was changed to aureomycin, 250 mg. four times a day.

On Nov. 7, 1950, all lesions had involuted. She had received 267 capsules of chloramphenicol and 257 capsules of aureomycin. She insisted upon receiving the aureomycin because she said she "felt much better" and "her appetite had increased."

GROUP 3

Group 3 includes patients in whom lesions had improved, some having almost completely regressed; but when improvement stopped during chloramphenicol therapy, these patients objected to taking the capsules and disappeared from observation.

CASE 8.—F. R. J., a 33-yr.-old white woman whose condition consisted of numerous lesions on the face, had the eruption for four months. She had not received any treatment. Treatment with chloramphenicol capsules was begun on May 29, 1950. Improvement was apparent up to June 5, but thereafter not only was there no further improvement but also a few new lesions had appeared, and she discontinued treatment on June 19 and has not returned. She had taken 93 capsules.

CASE 9.—F. J., a 44-yr.-old married Negro man, was admitted in August, 1949, with six lesions on the right side of the face, the largest lesion 4 to 5 cm. in diameter. He had already been given three injections of bismuth subsalicylate without improvement.

Treatment with chloramphenicol was begun. By July 17, 1949, he had taken 224 capsules, and although there was improvement, two of the lesions having almost entirely regressed, the patient was not satisfied and stopped treatment. He was seen nine months later, but there was no change in his condition.

CASE 10.—D. R. B., a 30-yr.-old married white woman, was admitted Jan. 21, 1950, having had the condition for eight months. She had received elsewhere "several" intravenous injections of "gold" and intramuscular injections of bismuth, without benefit. Treatment with chloramphenicol, 1 gm. a day, was begun. She lapsed treatment March 4, having taken 140 capsules. After a follow-up request to continue treatment, she returned June 14, showing marked regression of lesions. She was "given" more capsules but decided she was satisfied with the improvement and discontinued treatment.

CASE 11.—C. R. D., a 47-yr.-old married white man, was admitted Oct. 5, 1950, having had chronic discoid lupus erythematosus for one and one-half years. He had received elsewhere 13 intravenous injections of gold sodium thiosulfate without improvement. Chloramphenicol therapy was begun, with a dosage of one 250-mg. capsule five times a day and an intravenous injection of 500 mg. once a week. Because of a local intravenous reaction he took only four such treatments. On Oct. 25, he showed definite improvement. On Dec. 13, there was still further improvement with almost complete regression of the several lesions on the left side of the neck. At this time he warned he would have to discontinue treatment in two weeks, as he was leaving town. Before leaving he returned for a final visit, and the improvement was marked. The lesions (12 in number) on the right side of the face and neck were markedly improved, and the patient promised to have his physician in Texas "watch" him while he continued his treatment. He had taken 266 capsules and had been given four intravenous injections of 500 mg.

GROUP 4

In Group 4 are three patients in whom all lesions completely regressed under treatment but who suffered a relapse which chloramphenicol alone could not control.

CASE 12.—K. B., a 34-yr.-old white, married woman, was first admitted Oct. 14, 1933, presenting several lesions of the face and scalp of five-years' duration. Up to that time she had received 77 intravenous injections of gold sodium thiosulfate, 11 intramuscular injections of bismuth arsphenamine sulfonate (bismarsen®), and 14 of bismuth subsalicylate. She had also had four carbon-dioxide-snow treatments. Only the cryotherapy was at all beneficial. She returned on Aug. 9, 1949, with a recurrence consisting of two lesions, one on the buccal surface of the upper lip and one on the vermilion border of the lower lip. Chloramphenicol was prescribed. Up to Oct. 19, 1949, she had taken 250 capsules, and both lesions had completely regressed.

On Feb. 11, 1950, she returned, presenting a relapse of the lesion on the buccal surface, and four new lesions, two on the vermilion border of the lower lip and two on the skin of the upper lip. Up to Dec. 16, 1950, she had taken 462 more capsules of chloramphenicol, five intravenous injections of gold sodium thiosulfate, and two intramuscular injections of bismuth subsalicylate, without satisfactory improvement. Results of urinalysis were normal, and serologic reactions were negative for syphilis. She stated that she would permit cryotherapy after the New Year.

CASE 13.—M. S., a 42-yr.-old married white woman, was first admitted on Oct. 16, 1945. She had two lesions, one on the buccal surface of the left cheek, 3 cm. in diameter, and one on the anterior surface of the nose, 3.5 cm. in diameter. She had received "some treatment elsewhere." She was given one intramuscular injection of bismuth subsalicylate and 12 intravenous injections of gold sodium thiosulfate from Oct. 30, 1945, to Oct. 14, 1946. There was slight improvement from the gold therapy, but the patient refused further treatment. She returned June 30, 1949, and still had two lesions, the one on the buccal surface of the upper lip and one lesion involving almost the entire nose. Oral administration of chloramphenicol was begun in the following dosage: one 250-mg. capsule every two hours day and night (12 a day) for three weeks, then one every four hours during the waking hours (5 a day) for 14 weeks. The buccal lesion regressed after two weeks of treatment and has not recurred. Treatment was discontinued Oct. 17, 1949, both lesions having cleared up. The total number of capsules taken was 742. She returned Nov. 28, activity having recurred on the nose and the lesion having become larger. Chloramphenicol was again administered but had no effect. She has had four cryotherapy treatments, and has shown improvement.

CASE 14.—C. R., a 34-yr.-old married white woman, was first admitted July 24, 1948, with lesions for which she had received elsewhere injections of penicillin and ultraviolet-ray treatments; after this treatment, the several lesions on the forehead and face had become larger, and new lesions had appeared on the trunk and upper extremities. Treatment with tablets of bismuth sodium triglycollamate was prescribed. In one month the lesions had improved. The patient lapsed treatment. She returned Sept. 17, 1949, the lesions having become more numerous and active. Oral chloramphenicol therapy was begun, and from Sept. 17 to Nov. 28 she took 328 capsules and presented almost complete regression of lesions, leaving only pinkish pigmentation. When she returned complaining of itching, oral aureomycin treatment was prescribed, and from Dec. 5 to Jan. 3, she took 250 mg. four times a day, 112 capsules. She returned April 14, 1950, with a recurrence, and chloramphenicol was again prescribed, and by Aug 17, 1950, she had taken 168 more capsules without improvement. She is now being treated with applications of liquefied phenol once a week and intramuscular injections of bismuth subsalicylate, without improvement.

GROUP 5

There are two patients in Group 5, both of whom at first improved under treatment with chloramphenicol, but the lesions did not completely regress. Instead, while taking chloramphenicol, the patients began to complain of itching, malaise, and loss of appetite. They were immediately hospitalized, and in spite of various procedures, including transfusions, died, with a final diagnosis of acute disseminated lupus erythematosus. Their cases follow in detail.

CASE 15.—M. L., a 28-yr.-old single Negro woman, was first seen April 23, 1949. There were four lesions on her face; the largest, 4 cm. in diameter, had been present for five years. She had had only ointment therapy in the past. Serologic test for syphilis elicited a negative reaction; urinalysis revealed a trace of albumin and no casts. One 250-mg. capsule of chloramphenicol four times a day was prescribed. On Sept. 3 there were a few new lesions on the back and chest. On Sept. 10, my note states that all lesions were markedly improved, with loss of infiltration and loss of color. On Sept. 24, the note reads, "eruption has become markedly aggravated, the lesions on the face have become more extensive, and more numerous on the chest and back. There is swelling of the legs and feet." The temperature was 100 F., pulse rate 76, blood pressure 132/78. Results of urinalysis were as follows: color, orange-yellow, cloudy; reaction, acid; albumin, 4+; sugar, 1+. Up to this time she had taken 140 capsules of chloramphenicol. The patient was immediately hospitalized (Sept. 24). A clinical impression of acute disseminated lupus erythematosus was made; tissue was removed for biopsy, and this impression was confirmed.

Hospital notes were as follows: On admission the patient had a profuse scaly eruption. Her temperature was 100.6 F. The skin was hot, dry, and shiny. There was a foul odor to her breath. The tongue was heavily coated. There was a firm tender node just posterior to the left-mastoid area. Results of chest examination were normal. Examination of the heart elicited a faint blowing murmur at the pulmonic area and a harsh murmur at the mitral area.

Laboratory report on the blood was as follows: red cell count, 4,480,000; white cell count, 5,450, with a normal differential count. Urine examination revealed a specific gravity of 1.027; albumin, 4+; sugar, 0; white blood cells, 1 to 2; red blood cells, 0, and numerous hyaline and granular casts.

Phenolsulfonphthalein and tuberculin patch tests elicited negative reactions. A roentgenogram showed slight heart enlargement. The electrocardiogram was normal. The temperature ranged in a spike-like manner from 99.6 to 102 F.

On Oct. 1, administration of chloramphenicol was tried again, but the patient became nauseated and vomited. The same reaction occurred on Oct. 5, and chloramphenicol treatment was discontinued. On Nov. 11 she complained of tender painful joints. On Nov. 12 numerous painful blebs appeared on the lesions over the body (Fig. 3) ranging in size from 1 to 3 cm. in diameter. She looked and felt toxic. Since urea nitrogen had risen to 72 mg. and her urinary output was decreased, and since she had been showing 4+ albumin with occasional showers

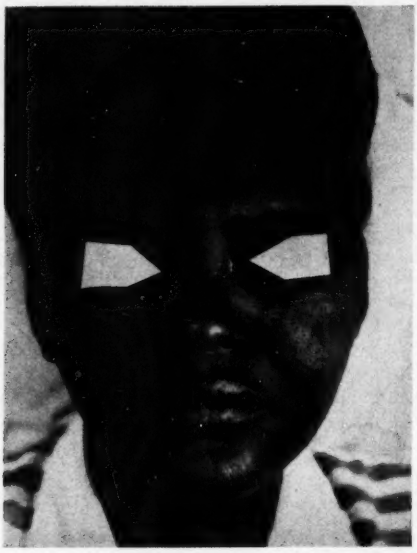

Fig. 2.—M. L. (Case 15), chronic discoid lupus erythematosus of five-years' duration.

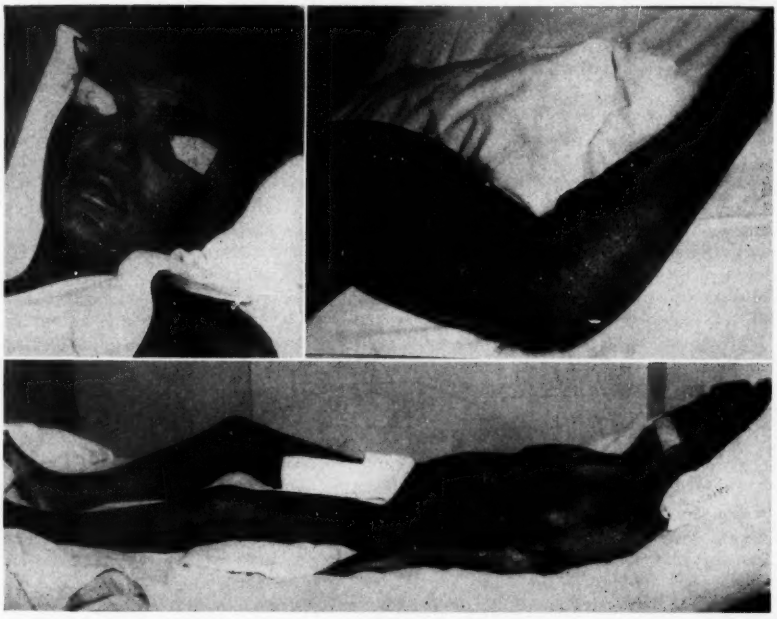

Fig. 3.—M. L. (Case 15), acute disseminated lupus erythematosus precipitated after taking 140 capsules of chloramphenicol.

of red blood cells, always having casts in her daily urine, she was given 1,000 cc. of 10% glucose intravenously daily. The blood culture was negative.

It was thought that she showed evidence of renal exhaustion, and corticotropin was administered. Because of a red painful throat she was given aureomycin, but this was discontinued after two doses. Skin lesions and bullae regressed, but an infarct developed in the right lung. Then both legs became swollen. In a week the lung infarct had cleared up and the edema of the legs completely subsided. On Jan. 28, 1950, the patient was discharged, as she felt comparatively well and insisted on going home. One week later she died, and permission for autopsy could not be obtained. During her stay in the hospital her albumin-globulin ratio on seven occasions was as follows: 3.31 to 2.11, 4.33 to 1.94, 3.53 to 2.17, 3.93 to 2.23, 2.68 to 3.19, 2.68 to 2.91, and 2.68 to 3.29.

Case 16.—P. R., a 45-yr.-old married Negro woman, was first seen in January, 1949, in the University Hospital, where her condition was diagnosed as chronic discoid lupus erythematosus, and I was asked to watch her as she was being given paraaminobenzoic acid. From April 23 to May 2 she received 182 gm. at the rate of 2 gm. every two hours. From April 30 to May 6 she had a rise in temperature ranging from 100 to 105 F. After two and one-half days of fever under paraaminobenzoic acid therapy, use of the drug was discontinued, and her temperature immediately fell to normal. She was given one injection of bismuth subsalicylate. None of this medication caused improvement of the lupus erythematosus lesions. Serologic tests for syphilis elicited doubtful reactions. Results of urinalysis were normal. On Aug. 23 she returned, and oral administration of chloramphenicol was begun. On Oct. 18, 1949, she had taken 182 capsules, and all lesions had improved. Results of urinalysis were normal. Her temperature was 99 F.

Because she complained of itching, she was given one of the antihistaminic drugs ("foralamin"), which she believed increased the itching. From Nov. 8, 1949, to Nov. 29, she took 83 more capsules of chloramphenicol, but this time the lesions failed to improve, although there were no new skin lesions. From Dec. 13 to Dec. 27, she took 56 capsules of aureomycin, each 250 mg. On Jan. 10, 1950, she complained of malaise, and her temperature was 99 F. On February 20 lesions had become more numerous and covered the face, chest, and back. On April 1, 1950, she was hospitalized because of vaginal bleeding, severe weakness, shoulder pains, and the skin lesions. Temperature on admission to the hospital was 101.4 F., pulse rate was 112, and blood pressure was 130/60. The skin lesions tended to confluency, although atrophy and follicular plugging were easily noted. There was periorbital edema.

Aside from the skin lesions, physical examination elicited no abnormalities, except that there was an aortic and mitral systolic blowing murmur, and on the cervix uteri there were several erosions.

On April 21, after an impression of acute disseminated lupus erythematosus was made, she was given cinchoninic acid, 1 gm. daily. In one week there was a fall in temperature from 103 to 101 F. Appetite continued to be poor. On April 20, the platelet count was 7,200, and she was given, up to April 28, three whole-blood transfusions. Examination of catheterized urine revealed albumin (2+). Blood cultures on several occasions were negative. By April 28, she showed some symptomatic improvement and was able to bathe herself. On May 1, she began having rises in temperature to 103 F., and she had urinary urgency and dysuria. Upon catheterization the urine was found to be grossly bloody. Cinchoninic-acid therapy was again started, this time concurrently with aureomycin. This medication was stopped after three days. On May 15, she complained of swollen legs. By this time she had received "twenty" transfusions without definite elevation in the hemoglobin. Cinchoninic-acid therapy was begun again May 20, but, as there was no response in lowering the temperature or reducing the leg edema, it was discontinued. A culture of the catheterized urine produced a "pure culture" of Escherichia coli. She was then given streptomycin, but on June 12 its use was discontinued, and instead terramycin was given, from which a mild diarrhea developed. On June 21 urine was fairly clear, but the culture produced hemolytic Staphylococci aureus. On July 4, the patient began to have gingival bleeding. The platelet count at this time was 3,100, hemoglobin 42%. On July 9 the patient became irrational and, after a four-hour period of coma, quietly died.

On April 28, the electrocardiogram indicated anterior myocardial injury, possibly infarction.

On admission the white blood cell count was 4,400, with 76% polymorphonuclear leucocytes and 34% lymphocytes; the red blood cell count was 3.3, hemoglobin 64% (9.5 gm.). The leukopenia continued up to May 15, when the white blood cell count rose to 10,500, and on May 22 it was 15,500.

On admission examination of urine showed no sugar nor albumin, and a specific gravity of 1.001. On May 1 the urine showed numerous white blood cells and 3+ albumin. On April 12 Escherichia coli were present; globulin was 3.64, and albumin 3.48. On April 20 the albumin-globulin ratio was 2.9 to 3.48, and May 31 it was 3.76 to 5.14.

After autopsy the diagnosis by the pathology department was acute disseminated lupus erythematosus; vasculitis (capillary, arteriolar, venule), chronic disseminated; encephalitis, focal, necrotizing, disseminated (disseminated lupus erythematosus, cerebri); hemorrhage, intracerebral, focal, diffuse; hemorrhage, subarachnoid, focal, diffuse; calcification, falx; skin, acute lupus erythematosus, disseminate type.

SUMMARY

Sixteen patients with chronic discoid lupus erythematosus have been treated with chloramphenicol (chloromycetin®). Fifteen were treated orally, receiving 1 to 1.25 gm. a day, divided into 4 or 5 doses of 250 mg. each. One received combined oral and intravenous chloramphenicol therapy. Of the 16 patients, all but one showed some change. Of the remaining 15, four showed moderate to marked improvement, but the condition became stationary or the patients had to leave town, and these patients finally discontinued treatment. Six were "cured," in the sense that all lesions completely regressed and at this time have not recurred. There were three patients in whom all lesions regressed under treatment, but in less than three months lesions recurred and did not respond to chloramphenicol, bismuth, or gold therapy.

The condition of two patients changed from the chronic discoid type of lupus erythematosus to the acute disseminate (systemic) type, as proved by biopsy and other laboratory findings. Both died, although one had improved cutaneously and systemically and was permitted to go home, where she died in a week's time from a cerebral embolus.

106 E. Chase.

CORTISONE ACETATE ADMINISTERED ORALLY IN DERMATOLOGIC THERAPY

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OUR EXPERIENCE confirms that of others,[1] showing that oral administration of cortisone acetate is as effective as its administration by intramuscular injection. This circumstance is of great importance to every physician and private practitioner; and it is especially important to the dermatologist, who treats a large proportion of his patients in an ambulatory state.

It therefore appears indicated at this time to present a brief review and evaluation of our experiences with the therapeutic effectiveness of orally administered cortisone acetate in various dermatoses. A total of 32 patients from the private practice of one of us (M. B. S.) are reported upon in the accompanying table. These represent all the patients treated by this modality since October, 1950, when we began administering cortisone acetate by the oral route.

At first, the hormone was prepared for oral administration by mixing the cortisone acetate solution[2] with equal parts of isotonic sodium chloride solution in such a way that one teaspoonful (4 cc.) contained 50 mg. of cortisone acetate. Later, raspberry syrup was substituted for the saline solution in an attempt to disguise the bitter taste of the preparation. When larger doses were required, the solution (25 mg. per cubic centimeter) was given undiluted; when smaller doses were required, one part of the cortisone acetate solution was diluted with three parts of the diluent with the result that one teaspoonful (4 cc.) contained 25 mg. In order to control the dosage carefully, it was, of course, important that measuring

Merck & Company, Inc. (Dr. Augustus Gibson, Executive Director, Medical Division), supplied some of the cortisone acetate used in this study.

1. (*a*) Boland, E. W., and Headley, N. E.: Oral Use of Cortisone Acetate, J. A. M. A. **145**:8-11 (Jan. 6) 1951. (*b*) Freyberg, R. H.; Patterson, M.; Adams, C. H.; Durivage, J., and Traeger, C. H.: Practical Considerations of the Use of Cortisone and ACTH for Rheumatoid Arthritis, read before the American Rheumatism Association, San Francisco, June 23, 1950, to be published; cited by Boland and Headley.[1a] (*c*) Hench, P. S.: in discussion on Freyberg and others.[1b]

2. "Suspension cortone acetate with benzyl alcohol 1.5%" (Merck & Company, Inc.), as prepared for intramuscular use, containing 25 mg. cortisone acetate per cubic centimeter of normal saline.

The Results of Therapy with Orally Administered Cortisone Acetate in Various Dermatoses

Case	Sex	Age	Diagnosis	Duration of Disease	Response to Previous Therapy	Initial Daily Dose (Mg.)	Subsequent Daily Dose (Mg.)	Response to Oral Cortisone*	Duration of Cortisone Therapy† (Days)	Course After Stopping Cortisone	Remarks
1	F	12	Atopic dermatitis	11½ yr.	Poor	100 for 5 days	75	Excellent	14	Recurrence	Breakthrough under 75 mg. daily
2	F	35	Atopic dermatitis	10 yr.	Poor	200 for 9 days	100 gradually reduced to 12.5 every other day	Excellent	120	Therapy continued	Hyperpigmentation of face, neck, chest, and arms; lessened as dose reduced
3	F	20	Atopic dermatitis	19½ yr.	Poor with older measures; excellent with ACTH 75 mg. daily	150 for 5 days	100	Excellent	23	Recurrence	Breakthrough under 100 mg. daily; excellent response with 50 mg. cortisone acetate orally and 25 mg. ACTH intramuscularly daily
4	M	26	Atopic dermatitis	16 yr.	Fair to poor	200 for 3 days	75	Good	99	Therapy continued	Breakthrough under 75 mg. daily; 25 mg. ACTH intramuscularly substituted for cortisone acetate every 7th day
					.....	.....	200	Excellent	...	.....	Excellent response maintained on 150 mg. daily
5	F	24	Atopic dermatitis	24 yr.	Good at first; recently poor	200 for 2 days	100, then 50	Good	8	Mild recurrence	Therapy discontinued because of mildness of recurrence and history of pulmonary tuberculosis
6	M	26	Atopic dermatitis	19 yr.	Good to poor	50 for 45 days	100 gradually reduced to 50	Excellent	91	Therapy continued	Therapy started with 50 mg. cortisone acetate orally and 25 mg. ACTH intramuscularly per day; when this decreased, breakthrough occurred; maintained on 50 mg. cortisone acetate daily
7	M	47	Atopic dermatitis	30 yr.	Excellent to poor	150 for 3 days	100, then 75	Excellent	17	Therapy continued	Condition excellent when patient stays in Southwest; slight breakthrough under 100 mg. daily
8	F	33	Atopic dermatitis	33 yr.	Good to poor	150 for 3 days	100, then 75	Good	20	Therapy continued	Complained of "excess energy" and difficulty in getting to sleep
9	F	18	Atopic dermatitis	17½ yr.	Good to poor	150 for 1 day 150 for 2 days	100 100, then 75	Excellent Excellent	2 9	Recurrence Therapy continued	....
10	M	36	Atopic dermatitis	15 yr.	Good to poor	150 for 14 days	100	Fair	21	Therapy continued	.....
11	M	34	Atopic dermatitis	30 yr.	Good to poor	200	200 gradually reduced	Excellent at first; poor later	14‡	Recurrence	Began breakthrough a few days after discharge from hospital while still on 200 mg. daily

12	F	34	Atopic dermatitis?	17 yr.	Fair to poor	100 for 3 days	50	Good	20	Therapy continued	Felt very "jittery" and "nervous" besides feeling "exhausted"; breakthrough under 50 mg. daily
13	F	51	Atopic dermatitis?	17 yr.	Poor	150 for 3 days	100 gradually reduced to 25	Excellent	21	Therapy continued	Breakthrough under 50 mg. daily; dose reduced because of increased blood pressure
14	F	60	Atopic dermatitis?	4 yr.	Good to poor	133 for 5 days	50	Excellent	104	Therapy continued	Breakthrough when cortisone acetate temporarily stopped because of rise in blood pressure; blood pressure dropped in spite of restarting cortisone acetate
15	F	54	Nummular eczema	2 yr.	Poor (in most recent attack)	150 for 6 days	100	Good	14	Recurrence	Breakthrough under 100 mg. daily
16	M	55	Dermatitis herpetiformis	10 yr.	Poor (in most recent attack)	150 for 3 days	150 gradually reduced to 50	Excellent	40	Recurrence	Breakthrough when cortisone acetate temporarily stopped; itching abated when 150 mg. per day was resumed
17	M	73	Dermatitis herpetiformis?	3 mo.	Good to poor	200 for 7 days	100	Excellent	21	Therapy con tinued	Breakthrough under 100 mg. daily
18	F	44	Urticaria (penicillin)	12 days	Poor	200 for 1 day	50	Excellent	23	Remained clear	Recurrence when cortisone acetate stopped for 2 days; for a short period, 50 mg. of cortisone acetate given orally every other day and 25 mg. ACTH intramuscularly on alternate days
19	M	42	Urticaria (penicillin)	1 mo.	Poor	100 for 2 days	25	Excellent	13	Few new lesions for 10 days	Recurring lesions controlled by 25 mg. daily for 2 days; no subsequent recurrence
20	M	58	Distinctive exudative discoid and lichenoid chronic dermatosis	8 wk.	Poor	200 for 8 days	150 gradually reduced to 100	Good	21	Therapy continued	Had previously received 500 mg. of cortisone acetate intramuscularly over a 9-day period with no relief
21	M	49	Distinctive exudative discoid and lichenoid chronic dermatosis	3 mo.	Fair to poor	50	50	Excellent	13	Recurrence after one week	Cortisone stopped by family physician because of 10-point rise in blood pressure; flare-up responded within 24 hr. to 100 mg.
22	M	56	Generalized pruritus, etiology unknown	6 yr.	Poor	200 for 3 days	50	Good	6	Therapy continued	.....
23	M	59	Pruritus ani; radiodermatitis(?); psoriasis(?)	25 yr.	Poor	100	100	Good	18	Recurrence	Concomitant topical therapy started at same time as oral cortisone acetate
						100	100	Fair	19	Recurrence	Cortisone stopped because patient complained of dizziness

The Results of Therapy with Orally Administered Cortisone Acetate in Various Dermatoses—Continued

Case	Sex	Age	Diagnosis	Duration of Disease	Response to Previous Therapy	Initial Daily Dose (Mg.)	Subsequent Daily Dose (Mg.)	Response to Oral Cortisone*	Duration of Cortisone Therapy† (Days)	Course After Stopping Cortisone	Remarks
24	M	18	Eczema cruris; psoriasis(?)	7 days	Poor	150 for 3 days	75	Poor	12	Recurrence	.....
25	M	6½	Psoriasis	4 yr.	Poor	75	133 gradually reduced to 25	None	36	Unchanged	Itching relieved almost immediately, lesions unchanged; dose of cortisone acetate lowered while daily insulin given
26	M	73	Stasis dermatitis with "autoeczematization"	3 yr.	Poor	200 for 1 day	100 gradually reduced to 25	Excellent	33	Remained clear	Concomitant topical therapy started at same time as oral cortisone acetate
27	F	28	Erythema annulare centrifugum	11 mo.	Excellent with ACTH 100 mg. daily	200 for 3 days	150 gradually reduced to 75	Excellent	52	Therapy continued	Stated that breasts became smaller after starting cortisone acetate; also happened with ACTH
28	F	51	Pemphigus foliaceus	2 mo.	Good to none	285	285	Poor	14	Recurrence	Moon facies developed; had previously had ACTH; subsequently excellent response to 300 mg. injections of ACTH daily
29	F	32	Pemphigus vulgaris	2 mo.	Poor to none	300 for 6 days	300 gradually reduced to 25	Excellent (combined with other therapy)	95	Therapy continued	Manifested moon facies, 20-lb. (9.1-kg.) gain in weight and hypertrichosis; had previously received ACTH; face less round when last seen; on daily insulin and suramin sodium for short intervals
30	M	51	Herpes zoster	30 days	Poor	200	200	None	3	Unchanged	.....
31	F	44	Filiform warts	5 mo.	None	75	75	None	4	Unchanged	.....
32	F	22	Plantar warts	2 yr.	Poor	200 for 3 days	100	None	7	Unchanged	.....

* Excellent, 90-100% improvement; good, 75-90% improvement; fair, 50-75% improvement; poor, 0-50% improvement.
† Duration of therapy on cortisone acetate is figured through Feb. 1, 1951, when data were compiled for publication.
‡ After this time the patient was followed by another physician, who reported breakthrough with 200 mg. daily.

teaspoons be used or that the patient know how to measure exactly 4 cc. of the solution. When tablets [3] were made available, administration of the drug was greatly simplified.

In our series of patients with selected and severe dermatoses, a trial of cortisone acetate administered by mouth was considered warranted when older therapeutic approaches had failed, and when careful history and general physical and laboratory examinations failed to disclose any known contraindications, i. e., no diabetes, hypertension, renal disease, or psychosis, or familial history of any of these.

Among the principal purposes for which we administered cortisone orally were the following: (1) to get the patient "over the hump" of the acute phase of a dermatosis, e. g., atopic dermatitis, dermatitis herpetiformis, nummular eczema, distinctive exudative discoid, and lichenoid chronic dermatosis of Sulzberger and Garbe; (2) to give relief from the annoying, incapacitating, or dangerous symptoms and lesions of an acute or chronic dermatosis, such as a penicillin urticaria or multiform drug eruptions, even though the condition was one which could be predicted to be "self-limited"; (3) to afford relief while a dermatosis, such as severe pruritus ani or vulvae or generalized pruritus, was being investigated further; (4) to get a dermatosis "under control" so that other forms of therapy could be used effectively; (5) as a purely temporary measure of practical usefulness; for example, to make a patient able to travel and thus move to a section of the country where persons with similar dermatoses are known to do well (e. g., in cases of atopic dermatitis, distinctive exudative discoid and lichenoid chronic dermatosis); (6) to help a patient meet an "emergency," such as a wedding or debut party, where he must look and feel well "at all costs"; (7) to produce and maintain remissions in diseases in which the eventual prognosis is very poor (as in pemphigus vulgaris or subacute and acute disseminated lupus erythematosus) by means of continued administration of the lowest effective doses.

PROCEDURE

Prior to the start of oral administration of cortisone acetate to an ambulatory patient, blood pressure and weight were recorded, and a urinalysis was done. During the period of administration, these examinations were repeated weekly or biweekly. Moreover, patients were closely observed for other physical changes. Mental changes were looked for also, and patients were carefully questioned for subjective complaints at each visit.

For the majority of patients the starting dose varied between 100 and 200 mg. a day. Subsequent doses were determined by the patient's response and were adjusted accordingly. In all instances, regardless of whether the dermatosis were a benign or a fatal one, it was the policy to reach the lowest effective daily dose as rapidly as possible. In the majority of our selected cases, the response to the initial dose of cortisone acetate was quite spectacular. Within 24 hours, patients usually noted great subsidence of all symptoms; and clinical improvement was usually apparent in from 24 to 48 hours. Changes in the daily dosage were made most frequently in increments or decreases of 25 mg. per day, although occasionally larger or smaller steps were used.

3. "Tablets cortone acetate," 25 mg. (Merck & Company, Inc.).

When oral administration of cortisone acetate was prescribed, patients were permitted to continue topical medications being used at the time. If other oral preparations were being taken previously, such as antihistaminics, antibiotics, or vitamins, their use was discontinued in most instances. It was obvious, then, to both the patient and to us that the rapid subjective and objective improvement resulted from the addition of the cortisone acetate to an existing therapeutic regimen which had not in itself brought satisfactory relief.

For patients receiving the hormone over a prolonged period, salt-poor diets were prescribed and each of these patients was given 3 gm. of potassium chloride daily by mouth.

When indicated, maintenance doses have been continued provided that the patients could be followed regularly and periodically. Cortisone acetate treatment was stopped in most cases after a variable time for the following reasons: (1) clearing of lesions with no recurrences after cessation of therapy; (2) clearing of lesions during cortisone acetate therapy and subsequent control by topical therapy; (3) suspected or actual adverse effects of prohibitive degree; (4) patient's inability to return for follow-up visits; (5) failure of the drug to help.

ADVERSE EFFECTS

Out of a total of 32 patients studied, there were three who manifested objective adverse effects while taking cortisone acetate. In one patient (Case 28) a moon facies developed during treatment with the drug. This patient had previously received corticotropin (ACTH). Another patient (Case 29) also manifested a moon facies, with hypertrichosis and a gain of 20 lb. (9.1 kg.) while taking the hormone. She also had had previous therapy with corticotropin. Large doses of cortisone acetate following upon the large doses of corticotropin were thought justified in these two cases of pemphigus. As the dose of the cortisone acetate was reduced, the side-effects became less apparent. In the third patient (Case 2), a light-brown hyperpigmentation of the face, neck, upper chest, and arms developed. As the dose was reduced, the pigmentation gradually became less evident.

Elevation in blood pressure noted in three patients (Cases 13, 14, and 21) could not be proved to be the result of administration of cortisone acetate, although the chronologic sequence made this appear likely. Unfortunately, in none of these patients had an adequate "base line" of blood pressure been determined before administration of the hormone. Whatever the cause in these three cases, our own observations confirm the general opinion that cortisone acetate will not usually cause a change in blood pressure. One patient (Case 23) stopped the drug because of dizziness. Again, it is not known whether the cortisone acetate had anything to do with this complaint. Two patients (Cases 8 and 12) complained of a definite hyperexcitability and insomnia.

SUMMARY AND CONCLUSIONS

1. Thirty-two patients with various severe or selected dermatoses were chosen for treatment with cortisone acetate by mouth.

2. The criteria for selection included refractoriness to previous therapy and absence of ascertainable contraindications.

3. The initial dose of cortisone acetate varied between 100 and 200 mg. per day.

4. The dose was reduced as quickly as each patient's response permitted, with the object of reaching the lowest effective dose as quickly as possible.

5. Response of most patients to the hormone was dramatic, with abatement of symptoms within 24 hours and substantial improvement of clinical signs within 24 to 48 hours. Details of the results are tabulated.

6. Adverse effects, possibly attributable to the hormone, were noted in five patients. In two instances, moon facies developed, one with hypertrichosis and a 20-lb. (9.1-kg.) gain in weight. However, both of these patients had received corticotropin (ACTH) prior to the cortisone. A third patient showed hyperpigmentation of the areas of skin usually exposed and not covered by clothing. Two additional patients each complained of hyperexcitability and insomnia. All these undesirable effects diminished or disappeared after the dose was reduced or administration of cortisone was discontinued.

7. The effectiveness of this new therapeutic approach in a wide variety of skin diseases is clearly demonstrated by the excellent response noted in this series of selected cases. No other modality known to us has comparable beneficial effects.

8. It is to be stressed, however, that the benefits generally stop soon after cortisone therapy is discontinued, unless the disease or the attack is one with spontaneous remissions.

9. Disagreeable and sometimes dangerous effects still preclude the use of this treatment except in serious diseases and situations, and unless the patient can be kept under sufficiently close and expert surveillance.

ADDENDUM

Since submitting this article for publication, we have continued to use cortisone acetate by mouth in the treatment of patients with selected dermatoses. Our enlarged experience with patients receiving cortisone acetate according to the outlined procedure, whether for short periods (several days) or prolonged (6 to 12 months) periods, has in no way altered our conclusions regarding the efficacy of the drug or the need for following the patient most carefully. When higher doses are used (200 to 1,000 mg. daily), as in pemphigus or acute disseminated lupus erythematosus, it is imperative that frequent examinations and necessary laboratory studies be insisted upon.

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BISMUTH PUTTY IN X-RAY SHIELDING

Efficiency of Material and Advances in Technique

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AND
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ONE OF US (J. W. W.) recently [1] recommended a putty composed of 84% bismuth subnitrate and 15% anhydrous wool fat to replace sheet lead for shielding the peripheral normal skin during treatment of a dermatologic lesion with x-rays. Since that article was submitted for publication careful measurements of the efficiency of this material in stopping radiation have been made, and additional experience, enhanced by critical evaluation of the method by several colleagues, has yielded improvements in technic.

EFFICIENCY OF MATERIAL

A sample of putty prepared according to the original formula was examined in the following manner:

Small portions were compressed between the plane surfaces of a hinged, two-bladed, wooden paddle so that discs varying from 1 to 5 mm. in thickness were produced. Each disc was prevented from adhering to the wooden surfaces by two sheets of cellophane. When these discs were cooled by being placed upon a metal plate resting on cracked ice, the putty became hardened sufficiently for accurate measurement of thickness to be made by using an ordinary micrometer. After much trial and error, five discs were ultimately prepared which, after the thickness of the two layers of cellophane was subtracted, showed no appreciable variation from the uniform thickness of 1, 2, 3, 4, and 5 mm.

A sheet of thin cardboard was arranged in a manner suitable to support these discs at a distance of 6 in. (15 cm.) from the target of a standard x-ray machine in current use for the administration of therapeutic radiation. Directly beneath this cardboard, the ionization chamber of the standard Victoreen instrument was installed. Using the various kilovoltages usually employed by dermatologists, measurements were made of the amount per minute of radiation passing through the cardboard and two layers of cellophane.[2] Discs of putty were then interposed, one at a time, between the beam and the ionization chamber and measurements taken after the addition of each disc. As an additional check the measurements made through the 3-mm.-thick disc were compared with those observed when the 1-mm. and 2-mm.-thick discs were used in combination, the 4-mm. with the 3-plus-1, and the 5-mm. with the 3-plus-2 and 4-plus-1. These

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From the Department of Dermatology, University of Southern California School of Medicine.

1. Wilson, J. W.: Shielding of Skin Against Roentgen Radiation by Plastic Compounds, Arch. Dermat. & Syph. **62**:237 (Aug.) 1950.

2. Mr. Louis F. Flores, of the Department of Radiology, Los Angeles County General Hospital, gave technical assistance in this phase of the study.

measurements were made in duplicate, one series by each of us, and were found to be in close agreement. All figures were converted into percentages of radiation allowed to pass through the putty disc.

From the data obtained by these measurements, the accompanying curves were plotted, each representing for a single kilovoltage the efficiency of various thicknesses of bismuth putty in stopping the radiation. The kilovoltages investigated covered the range ordinarily utilized by dermatologists (Fig. 1).

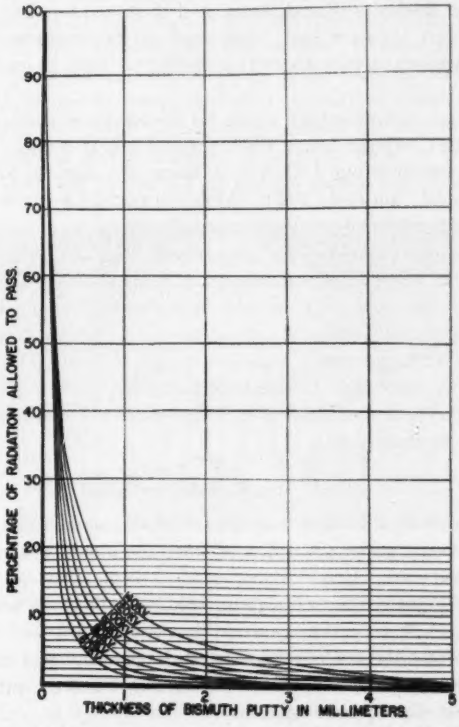

Fig. 1.—Efficiency of bismuth putty in stopping x-radiation at various kilovoltages, as measured by using the Victoreen ionization chamber.

INTERPRETATION OF RESULTS

It will be seen that a small percentage of radiation passes through this material, the amount increasing with higher kilovoltages. It must be recalled, however, that even solid metallic lead allows some radiation to pass, especially when used in the customary thin sheets from 0.5 to 1.0 mm. in thickness. Comparisons made of the efficiency of the putty as against sheet lead showed the former to be from one-third to one-fourth as radiopaque, the lower values pertaining to higher kilovoltages. That this figure is somewhat less than that predicted by calculations from the atomic weights of the ingredients was explained by the discovery that a certain amount of

air is entrapped in the interstices of the powder granules and becomes unavoidably included in the finished putty. Elimination of this feature, if it should prove possible, would make the putty more efficient; no feasible method has as yet been proposed.

It was clearly stated in the earlier report,[1] moreover, that the putty is not easily handled in thin layers, and the compression paddle which is advocated produces it in the form of a disc about 5 to 6 mm. in thickness. Measurements of the thinnest spots produced by manipulations of these putty discs by several operators in adapting the material to the contour of irregular lesions have shown 3 mm. to be the lower limit of thickness of such areas, and these are usually only the size of a fingertip. It is thus apparent that, when used in the recommended manner, the putty method furnishes at least as good a shield as 1 mm. of lead and much more than 0.5 mm.

Even at 140 kv. (a rather high figure for dermatologic therapy) only 1.5% of the radiation passes through 5-mm. thickness and 4% at 3 mm. At this intensity, for example, in administering 4,000 r to a lesion, the shielded area might receive 50 to 60 r, and small, thin spots 160 r. While not negligible, these amounts present no danger.

Moreover, careful measurements have shown that at 140 kv. the small percentage of radiation which is allowed to pass consists of only the very hardest rays, possessing a half-value layer of 22 mm. Al. It is obvious that small portions of such hard radiation cannot harm the skin, since the erythema dose at this level approximates 1,000 r. When extremely high kilovoltage or heavily filtered radiation is employed, it is necessary only to use a thicker layer of putty to afford whatever degree of protection is desired, just as it is customary to use a thicker layer of lead under similar circumstances.

ADDITIONAL SUGGESTIONS IN TECHNIC

The most troublesome feature in technique of this method lies in the tendency of the putty to become sticky when it is warmed too much by handling or by high atmospheric temperature. Recent experiments indicate that the formula for the putty can soon be improved in this regard. Meanwhile it is necessary to emphasize that additional bismuth subnitrate powder should be added with the approach of summer to counteract the tendency toward stickiness, and that more of the same powder should be lightly dusted over the patient's skin and the surface of the putty before it is applied, if it appears necessary.

After considerable use the plastic-cloth sheets become covered with a closely adherent film of wool fat containing sticky bits of the putty; this makes it difficult to remove the sheets from the putty disc without distortion. This difficulty may be obviated by cleaning the sheets forcibly with a rough cloth followed by powdering. Since the plastic material is very cheap (about 30 cents per square yard), each 6-in. (15-cm.) square sheets costs less than 1 cent. It is economical, therefore, to replace soiled sheets with new ones rather than to clean them.

Since the previous communication, it has been found convenient to install a series of circular cutters nested one within the other in an appropriate cavity in the wooden paddle near the root of the handle (Fig. 2). This prevents loss or misplacement. The largest of these cutters is actually a cup, so that the entire set may

be lifted out at once and the individual cutters thrown out into the hand for selection.[3] It must be emphasized that the use of one of these cutters serves only to furnish an opening approximating that of the area of the lesion to be treated; this opening is then enlarged or made smaller by manipulation as desired.

It is often convenient, after cutting the opening, to remove both plastic sheets and take the disc in the hands for partial stretching of the opening before placing it upon the patient's skin.

It is well to emphasize that the plastic cloth can be stripped easily from the surface of the disc of putty only if it is bent sharply back upon itself so that the direction of pull is truly parallel with the surface. If there is any angulation, distortion will occur because of the tendency of the putty to adhere to the cloth. Use is made of this feature in removing the cut-out portion of putty. As the second cloth is being stripped off, when its folded edge reaches the periphery of the cut-out portion, the direction of pull is suddenly changed to form an angle of about 45 degrees or more with the parallel. This upward pull is continued only until the

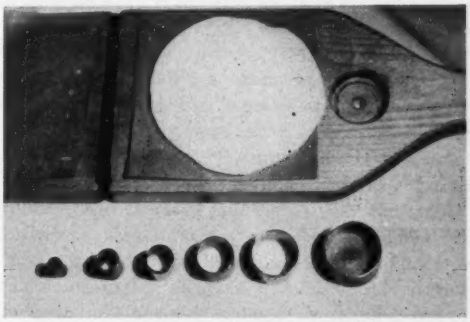

Fig. 2.—Compression paddle with circular cutters.

cut-out portion begins to follow by adhering to the cloth; then the former parallel direction is immediately resumed.

In shielding ringed lesions, such as granuloma annulare, the periphery is shielded, and then the small disc which was previously cut out of the putty may be manipulated to form an appropriate shield for the central uninvolved area.

In shielding linear lesions, such as keloids, it is advisable not to cut a circular opening in the putty disc but simply to score through it linearly with a dull object which will not damage the plastic cloth beneath. A tongue blade, applicator stick, or the rounded handle of the usual surgical scalpel will suffice. After removal of the second sheet of plastic cloth, the disc is taken in the hands and this linear cut expanded laterally as well as longitudinally to approximate the lesion. While the disc is still held between the hands, the opening may be advantageously tested for accuracy by bringing it close to the lesion; most of the adjustments may thus be made before the disc is allowed to touch the patient's skin.

3. This innovation was suggested by K. G. Ralls, Box 723, Station H, Los Angeles, who manufactures a satisfactory "paddle and cutter" set.

It has not been found possible to use this material beneath the eyelids for shielding the eyeball; it is not firm enough to resist being forced out of the fornix by the pressure of the lid against the eye. However, it is serviceable within the nares. A cylinder is inserted and then flattened out by pressure exerted on the outer surface of the nostril. The warmth of the nose causes the putty to become sticky, however, and the small aperture makes removal of this sticky mass difficult. This may be avoided by covering the original cylinder loosely with thin sheet rubber or plastic cloth. The putty can still be compressed and adapted to the cavity, but may be easily removed.

CONCLUSIONS

When used in the recommended manner, putty composed of 84% bismuth subnitrate powder and 16% anhydrous wool fat affords more protection against the passage of roentgen radiation than the lead sheets usually employed.

Improvements in the technic of handling the material are described.

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APPRAISAL OF THE TOXICITY OF SUNSCREEN PREPARATIONS

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IN ADDITION to the rays of the visible spectrum, sunlight contains rays of shorter wave length, those of the ultraviolet range. Coblentz and his associates [1] confirmed earlier work of Hausser and Vahle, and of Luckiesh, Holladay, and Taylor, establishing the fact that a maximal burn or erythemogenic effect in the skin was obtained per unit of energy absorbed at a wave length of 2,970 A. Another erythemogenic effect is obtained with rays of wave length 2,400 to 2,500 A. Rays with wave lengths ranging from 3,200 to 3,650 A. will "tan" (cause pigmentation) but not produce a burn. Sunscreen agents are products which upon topical application absorb or otherwise prevent actinic, erythemogenic rays of the sun from reaching the sensitive skin. Ideally, a sunscreen should permit the rays of the longer ultraviolet range responsible for "tanning" (pigmentation) to reach the skin.

Many chemical compounds have been found capable of absorbing the solar rays responsible for production of sunburn. Potential sunscreen agents represent chemical compounds differing widely in physical and chemical characteristics, and it is difficult to classify them into chemical families. Among the larger chemical groups are various derivatives of benzoic acid (esters of paraamino, orthoamino, orthohydroxy benzoic acid), pyrones, naphthosulfonic acids, naphthoic acids, and miscellaneous groups containing higher alcohols, quinine and derivatives, hydroquinone (orthodihydroxybenzene), sulfonamide compounds, tannins, and others.[2] The ideal sunscreen must not only possess the necessary ability to screen the undesirable, burning solar rays but also be relatively innocuous, per se, under all conditions of use.

PHARMACOLOGIC ASPECTS

A sunscreen preparation should undergo sufficient pharmacologic and toxicologic investigation to establish its safety under the most extreme conditions of use. This requires the procuring of data on (*a*) systemic toxicity following application to intact or damaged skin, (*b*) primary irritation, and (*c*) sensitization. Technics employed in this laboratory for the determination of toxicity of materials intended for topical application have been described elsewhere.[3] Sunscreens

From Division of Pharmacology, Food and Drug Administration, Federal Security Agency.

1. Coblentz, W. W.; Stair, R., and Hogue, J. M.: The Spectral Erythemic Reaction of the Untanned Human Skin to Ultra-Violet Radiation, Bur. Standards J. Res. **8**:541-547, 1932. Coblentz, W. W., and Stair, R.: Data on the Spectral Erythemic Reaction of the Untanned Human Skin to Ultra-Violet Radiation, ibid. **12**:13-14, 1934.

2. Giese, A. C.; Christensen, E., and Jeppson, J.: Absorption Spectra of Sunscreens, Am. Perf. & Essent. Oil Rev. **56**:3, pp. 197-201, 1950. De Navarre, M. G.: The Chemistry and Manufacture of Cosmetics, New York, D. Van Nostrand Company, Inc., 1941.

3. Draize, J. H.; Woodard, G., and Calvery, H. O.: Methods for the Study of Irritation and Toxicity of Substances Applied Topically to the Skin and Mucous Membranes, J. Pharmacol. & Exper. Therap. **82**:377-390, 1944.

are subjected to additional tests involving applications of sunscreen to skin previously damaged by sun or wind burn. A 21-day subacute dermal-toxicity experiment involves exposure to ultraviolet radiation immediately before the first application of sunscreen and twice weekly thereafter during the remainder of the 21-day experiment. The source of ultraviolet radiation used was a General Electric Uviarc portable A. C. ultraviolet outfit with an arc length of 6 in. (15 cm.) and giving 54 watts per arc inch. The initial (or preexperimental) radiation dose was made to the clipped intact skin of albino rabbits maintained at a distance of 12 in. (30.5 cm.) from the lamp for a period of 20 minutes. This radiation dose produced a marked erythema. The subsequent radiation doses were made under the same conditions, excepting that exposure time was reduced to 10 minutes.

Three sunscreen preparations representing compounds of different physical and chemical natures, namely, hydroquinone, tannic acid, and β-methyl umbelliferone, were examined for dermal toxicity. The solutions of these agents in the various solvents were (*a*) a 2% solution of hydroquinone in dimethyl phthalate, (*b*) a 5% solution of tannic acid in water, and (*c*) a 1% β-methyl umbelliferone preparation with the following composition:

	Per Cent (By Weight)
β-methyl umbelliferone	1.0
Propylene glycol	20.0
Ethyl alcohol	49.0
Water	30.0

These solutions were applied on albino rabbits for the following dermal toxicity tests: acute (single application), 21-day subacute, 21-day subacute with ultraviolet irradiation, and 90-day subacute. Sensitization studies were conducted on the albino guinea pig.

Our acute dermal toxicity experiments were conducted at three dosage levels of each solution, namely, 3.9, 6.0, and 9.4 ml. per kilogram of body weight. With the exception of a coagulative effect noted in the abraded skin areas of the animals treated with the tannic acid solution, no adverse local or systemic effects were observed in these acute dermal exposures.

In the 21-day subacute dermal tests, with and without ultraviolet irradiation, the daily dosage levels were 1.0, 2.0, and 4.0 ml., respectively, of each solution per kilogram of body weight.

No gross local or systemic effects were observed in the animals treated with the umbelliferone formula, or in the animals treated with the tannic acid solution. The animals treated with the hydroquinone solution exhibited an atypical dermatosis, which was aggravated by irradiation with ultraviolet rays. The dermatosis appeared at first as small petechiae, and was observed occasionally in a nontreated area of skin, suggesting that the reaction was an acquired sensitization. Edema of the skin was not noted.

In the 90-day subacute experiments, four dosage levels were used: 0.5, 1.0, 2.0, and 4.0 ml. per kilogram. The agents were administered by inunction daily to series of 12 rabbits for each of the three solutions. As in the 21-day subacute experiments, the subjects treated with the umbelliferone and tannic acid solutions exhibited no gross local or systemic effects following the 90-day treatment. Atypical dermatoses were observed in three of the 12 subjects treated with the hydroquinone solution. These atypical dermatoses were characteristic and appeared and disappeared several times during the course of the 90-day treatment. The initial reaction was always the very small petechiae in well-defined areas. As the lesion progressed the area exhibited an intense erythema. These dermatoses appeared at the three levels of dosage. Gross systemic effects were noted at the 2.0- and 4.0-ml. dose levels. There were subnormal body-weight gains, with slightly lowered food intake.

Sensitization Studies.—In view of the atypical dermatosis observed in the hydroquinone-treated animals, all three preparations were tested for potential sensitization by the guinea pig method.[8] No evidence of increased sensitivity to these agents was observed in any of three series of 10 guinea pigs employed.

Pathology.—No significant gross or microscopic change was noted in the animals treated with the umbelliferone preparation. Daily applications of the tannic acid solution produced a brown stain in the intact skin and no other evidence of gross change.

The animals treated with hydroquinone exhibited slight emaciation at the two higher dose levels. Microscopic examination revealed a moderate dermatitis and a very slight thyroid hyperplasia at the two higher dose levels, with decreases in these effects as the dosage was reduced.

COMMENT

Sunscreen preparations are unique, as cosmetics, in their manner of use. Their use at beaches, for example, may involve multiple and extensive daily applications to large areas of the total body surface. In addition, applications may also be made to skin already damaged by sun or wind burn. It is essential to obtain experimental toxicity data on the damaged as well as the intact skin. Sunscreen preparations may be used by persons of all age groups and in varying conditions of health. In view of this possible extensive use, it is necessary to have pharmacologic and toxicologic data to indicate an ample margin of safety in use. Data to establish such a margin of safety for the many compounds advocated as potential sunscreen material are not at present available.

Of the three agents investigated in this laboratory, we conclude that hydroquinone is not a suitable agent for use in sunscreen preparations.

SUMMARY AND CONCLUSIONS

Sunscreen preparations must possess the physical property of preventing the damaging rays of the sun from reaching the reactive skin. In addition, such preparations must not, per se, produce local or systemic harmful effects following normal topical use. Pharmacologic and toxicologic tests should establish an eight-fold margin of safety, and this entails acute and subacute dermal-toxicity and potential-sensitization studies. Such studies with tannic acid, β-methyl umbelliferone, and hydroquinone (orthodihydroxybenzene) have established that the last is an unsuitable agent for use in sunscreen preparations.

Dr. A. A. Nelson, pathologist, Division of Pharmacology, Food and Drug Administration, supplied data on gross and microscopic pathology.

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LICHEN CORNEUS HYPERTROPHICUS (LICHEN OCREAFORMIS, LICHEN OBTUSUS)

An Analysis of the Conditions with Which This Is Confused

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AND
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BROOKLYN

THERE is a skin condition affecting the legs almost exclusively which has been described under various and confusing names. It offers many difficulties in differential diagnosis from well-recognized diseases, and though not seldom seen is rarely discussed adequately, either because it is wrongly diagnosed or because it is uncritically passed over.

THE CLINICAL PICTURE

The dermatosis we refer to consists of irregular, but rather sharply defined, raised plaques of various sizes, composed of hemispherical, closely set, but usually discrete papules. The latter are split-pea-to-bean-sized, sometimes in bead-like arrangement, flesh-colored, dirty-gray-brown, ivory, or sometimes pinkish, chronic and recalcitrant to treatment, and intensely pruritic. The surface of the papules may be smooth or rough or even verrucous. They are set in plaques, often forming a mosaic, beyond which outlying papules may be found. The lesions are usually found on the ankles, particularly on the malleoli, shins, and calves, and rarely in the intergluteal fold and on the perianal area or on the medial aspects of the thighs. If of very long standing, the lesions may cover the leg from ankle to knee like a stocking.

HISTOLOGIC FEATURES

The horny layer is thick and compact and follows all the crests and indentations of a very rugose epidermis. The granular layer is increased in thickness. Acanthosis affects the rete pegs chiefly, and the suprapapillary plates are involved to a less extent. The vessels of the papillary and subpapillary zones are surrounded by banal inflammatory cells. The connective tissue shows sclerosis.

Secondary eczematization may be found; the cellular infiltrate in the cutis may be widespread, but the basal layer remains distinct. Exocytosis, edema, and parakeratosis are not found unless the lesions are eczematized. The suprapapillary plates may be thin, but other psoriasiform features are not found.

It would appear that the epidermis hypertrophies without a corresponding increase in connective tissue, and consequently the former becomes corrugated over the corium, giving the rather characteristic surface on microscopic examination.

From the Department of Dermatology and Syphilology of the Post-Graduate Medical School of the New York University-Bellevue Medical Center (Dr. Marion B. Sulzberger, Chairman), and the Skin and Cancer Unit of the New York University Hospital.

NOMENCLATIVE AND NOSOLOGIC PROBLEMS

It is because of the appearance in advanced cases that the name "lichen planus ocreaformis" was given by Lieberthal [1] in 1916 to the condition which he described, "ocrea" meaning a greave, or protective legging. It does appear as a sort of continuous armor in the picture of the condition in Lieberthal's articles.[2] The Suttons [3] reproduced it over the legend, "lichen planus (?) of extraordinary sort. 'Lichen

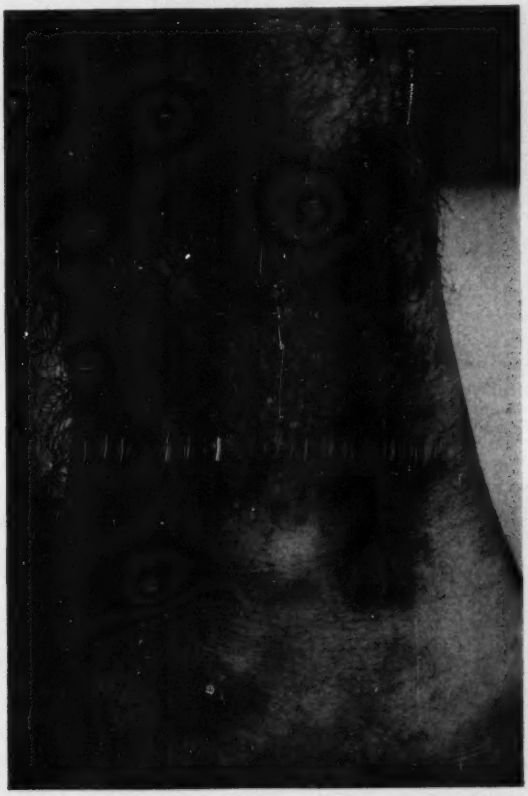

Fig. 1.—Plaque of lichen corneus hypertrophicus on medial aspect of right ankle of A. J. W., a man aged 22; eruption of 11 years' duration.

planus ocreaformis' of Lieberthal," although there is no description or discussion of the disease.

1. Lieberthal, D.: Shinguard Type or Lichen Planus Ocreaformis, J. A. M. A. **67**:1582 (Nov. 25) 1916.

2. Lieberthal, D.: Unusual Case of Lichen Planus, J. Cutan. Dis. **33**:395 (May) 1915.

3. Sutton, R. L., and Sutton, R. L., Jr.: Diseases of the Skin, ed. 10, St. Louis, C. V. Mosby Company, 1939, p. 313.

Fig. 2.—Photograph of section of skin of medial aspect of right ankle of A. J. W. (Fig. 1), showing hyperkeratosis, rugosity of the surface, acanthosis of rete pegs, sclerosis of connective tissue, and perivascular, banal cellular infiltrate. No amyloid was found with appropriate staining.

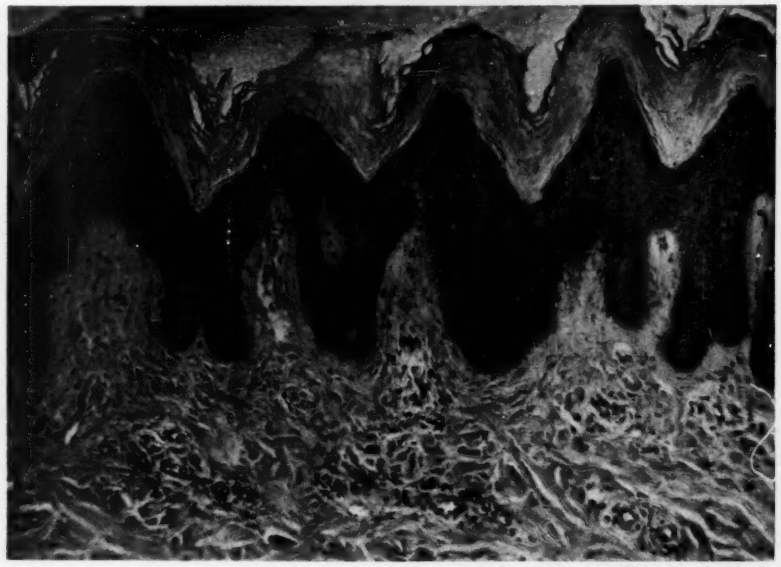

Fig. 3.—Photograph of section of skin of right shin of C. G., a man aged 27. No amyloid was found.

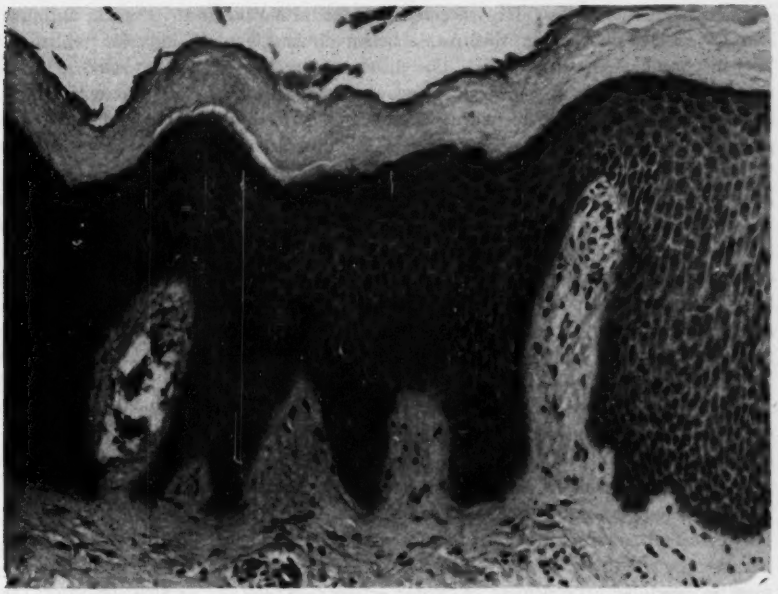

Fig. 4.—High-power photograph of section from lesion on left shin of V. H., a man aged 32; eruption of five years' duration. No amyloid was found.

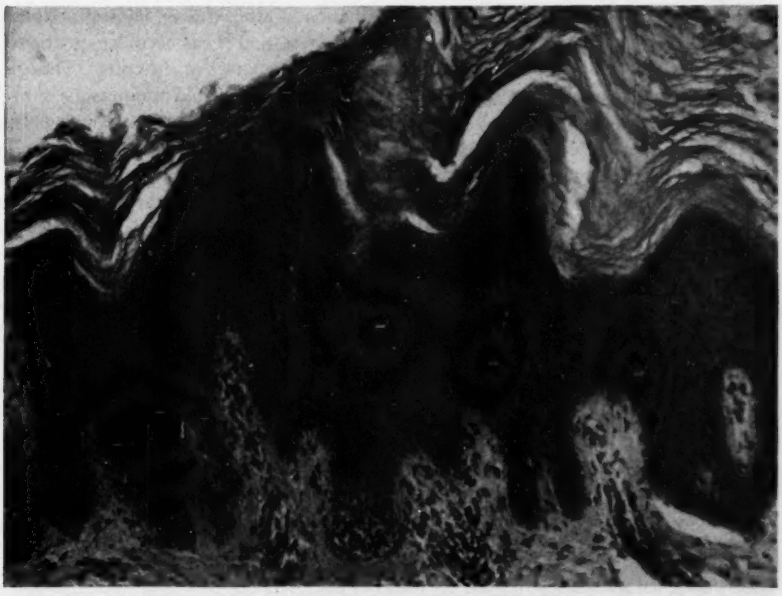

Fig. 5.—High-power photograph of section from lesion on left medial malleolar area of G. D. P., a man aged 30; eruption of seven years' duration. No amyloid was found.

The same dermatosis has received greater attention from French authors. Darier [4] discussed it under the name "lichen obtusus," while Pautrier [5] called it "lichen corneus hypertrophicus." The diseases with which this condition may be confused, and to which the dermatosis may in some cases be related, or with which some authors have sought to find connecting links, are the following: lichen planus, particularly the hypertrophic, verrucous, and "obtuse" varieties; lichen amyloidosus; lichen ruber moniliformis; lichen obtusus corneus (prurigo nodularis), and finally lichen chronicus simplex of Vidal.

The difficulties in differentiation are of three kinds: (1) those of clinical similarity; (2) those of similarity of name, due to insufficient knowledge of the various confusing conditions and the multitudinous names under which these several dermatoses have been described and discussed by different dermatologists, and (3) those of our unfortunate basic ignorance of the causes of almost all the dermatoses mentioned.

However, it will be granted that there are certain usually reliable criteria for some of these diseases. If a condition, which clinically might be "lichen obtusus," or hypertrophic lichen planus, or lichen amyloidosus, shows no histologic evidence of lichen planus when subjected to biopsy, and if reliable staining and mounting reveals no metachromatic amyloid, we may safely exclude the two latter diagnoses.

The resemblance between "lichen obtusus" and "lichen ruber moniliformis" (better called "morbus moniliformis lichenoides," as suggested by Wise and Rein,[6] because the condition is not lichen planus) is remote. In both there are, or there may be, bead-like arrangement of closely set papules; but, as we shall see later, the course, distribution, and histologic features of the two are very dissimilar.

"Lichen obtusus corneus," also known as prurigo nodularis of Hyde, shows nodule formation, at times almost tumor formation, scattered over the legs, thighs, and sometimes the arms. The nodules remain discrete, and it has been demonstrated by Pautrier that histologic sections show neuroma-like masses in the cutis. Though prurigo nodularis may be an individualistic response to repeated trauma, the similarity between "lichen obtusus" and "lichen obtusus corneus" is in names only, for clinically there is a vast difference between them.

Darier [4] points out that dermatoses consisting of obtuse [7] papules, which have been clinically called "lichen obtusus," are of three types: (1) lichen planus, (2) lichen ruber moniliformis, and (3) other obtuse papular dermatoses of the legs.

In Group 1, of course, the histologic features would be the deciding factor.

Group 2 he interpreted a a rare form of lichen planus in bead-like arrangement; but we have already pointed out that this bizarre dermatosis is not a variant of lichen planus. Those who use the term "lichen ruber moniliformis" for the "lichen obtusus" we are discussing, because of the bead-like arrangement that may be found in both diseases, are using one criterion only for the identification of the

4. Darier, J.; Civatte, A., and Tzanck, A.: Précis de dermatologie, ed. 5, Paris, Masson & Cie, 1947, p. 201.

5. Pautrier, L. M.: Lichénifications anormales, in Nouvelle pratique dermatologique, edited by J. Darier, Paris, Masson & Cie, 1936, Vol. 7, p. 521.

6. Wise, F., and Rein, C. R.: Lichen Ruber Moniliformis (Morbus Moniliformis Lichenoides), Arch. Dermat. & Syph. **34**:830 (Nov.) 1936.

7. "Obtuse" or blunt as applied to a papule conveys the sense of it being hemispherical or dome-shaped, not acuminate or pointed, not planus or flat.

condition preferably called "morbus moniliformis lichenoides," as mentioned above. Confusion has thus been created by the use of this term for a disease utterly different from the one it usually denotes.

Group 3 Darier would call "lichen obtusus," which he regards with Brocq and Pautrier as an idiosyncratic and individualistic response to scratching and therefore a form of "abnormal lichenification." He makes no mention of the difficulty of differentiation from lichen amyloidosus, which, in our experience, is the first clinical diagnosis usually offered and which is discarded only when, to one's surprise, no amyloid is found.

Prurigo nodularis has often been unnecessarily confused with "lichen obtusus" because one of the many synonyms for prurigo nodularis is "lichen obtusus corneus," a name given to it by Lailer and Brocq [8] in 1900. Darier [9] lists the following as synonyms for prurigo nodularis: lichen polymorphe ferox (Vidal); urticaria perstans verrucosa (Baker); urticaria perstans papulosa (Kreibich); urticaria chronica papulosa (Fabry), and possibly acne urticata (Kaposi). Gans [10] would simply relate these terms to various forms of the prurigos of Hebra.

According to Darier, although the individual lesion of prurigo nodularis may resemble that of "lichen obtusus," the two conditions show wide differences. Prurigo nodularis is distributed over the body and is not limited almost completely to the legs; prurigo nodularis is found at all ages, especially in women between 30 and 40 yr. old whereas "lichen obtusus" is found in older patients. We have seen the latter only in men, and six out of seven cases were in the 20-to-40-year age group. In prurigo nodularis there is a distinctive and heavy inflammatory cellular reaction in the cutis below the hyperkeratotic and acanthotic epidermis, which is not a feature of "lichen obtusus," as we have already pointed out. The important findings of Pautrier have been mentioned and will be discussed in greater detail later.

ILLUSTRATIVE CASES

At this point we give for purposes of clarification a résumé of the original articles of Lieberthal [11] concerning "lichen planus ocreaformis." No other papers on the subject seem to have appeared in American journals.

Lieberthal presented an "unusual case of lichen planus," which was later described in greater detail by him under the title "shinguard type of lichen planus ocreaformis," in a man of 63, who had a rash on the shins of six months' duration, which had been preceded by pain and vesiculation. The patient had densely set, pigmented, scaly, convex papules interspersed with angular flat ones, over the tibias from ankles to knees. There were some white spots on the buccal mucosa. Treatment with 4% chrysorobin externally and solution of potassium arsenite (Fowler's solution) internally resulted in great improvement. The histology was recognizable as resembling lichen planus.

Discussing the case, Schamberg thought it was one of prurigo nodularis; but White, who had described lichen obtusus corneus (prurigo nodularis of Hyde), and Zeisler dissented from this view. Arndt suggested the diagnosis of neurodermatitis.

8. Lailer and Brocq, cited by Pusey, W. A.: The History of Dermatology, Springfield, Ill., Charles C Thomas, Publisher, 1933, p. 202.

9. Darier, J.; Civatte, A., and Tzanck, A.: Précis de dermatologie, ed. 5, Paris, Masson & Cie, 1947, p. 710.

10. Gans, O.: Histologie der Hautkrankheiten, Berlin, Julius Springer, 1925, Vol. 1, p. 233.

11. Footnotes 1 and 2.

There seems little doubt that the case was one of lichen planus, with either (*a*) obtuse lesions of lichen planus, or (*b*) lesions of "lichen obtusus," which, as will be seen later in the presentation of Pautrier's views, may be associated with true lichen planus. It must, however, be borne in mind that amyloidosis cutis was unknown when Lieberthal described his case.

Now we shall give a running commentary on the following cases culled from transactions of various societies in the ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY, which indicate the lines of thought and the difficulties in diagnosis, at times almost insurmountable.

1. Fisher [12] presented a case of "lichen planus ocreaformis" in a white man, aged 47, with a resistant eruption of 29 years' duration on the legs from the ankles to the knees, which had recently spread above the knees. The entire front of the legs showed polygonal, shiny, violaceous, pink or yellow-pink, hard, infiltrated papules, forming sharply circumscribed plaques. Histologically there was no evidence of lichen planus. Fischer pointed out the "shinguard" appearance resulting from the setting of the papules, so that the legs appeared, as it were, paved with cobblestones. No mention was made of search for amyloid. In view of the histology the name "lichen ocreaformis" would have been more appropriate than "lichen planus ocreaformis," though of course the case may have been one of amyloidosis.

2. Sweitzer [13] presented a case of "lichen planus ocreaformis." A white woman, aged 68, had an eruption of 12 years' duration on the extensor aspect of the right leg from ankle to knee, consisting of a violaceous, dry plaque made of dime-sized, rough, very pruritic papules with whitish scales. The histology was that of lichen planus. Michelson in discussing the case accepted the diagnosis, saying it was a case of lichen ocreaformis, which, according to him, was a form of lichen planus and should be differentiated from neurodermite of Brocq and from prurigo nodularis.

Obviously this was an "ocreaform" type of lichen planus, a true "lichen planus ocreaformis," if this nomenclature is accepted, but not "lichen ocreaformis," which is a term that should be reserved for obtuse lichenoid dermatoses which are not lichen planus. On this basis Michelson might correctly have pointed out that "lichen planus ocreaformis" should be distinguished from neurodermite of Brocq. of which "lichen ocreaformis" ("lichen obtusus") may be a variant.

3. Greenhouse [14] presented a case of "lichen planus ocreaformis" in an Italian man, aged 67, who had an eruption of nine years' duration on the legs from ankles to knees. It consisted of discrete, purplish-red, lentil-sized papules with pigmentation, the lesions being hyperkeratotic near the knees. Histologically there was no evidence of lichen planus. There were hyperkeratosis, acanthosis, fibrosis, and a mixed cellular reaction in the cutis.

Gross and Satenstein both expressed the opinion that the case was one of circumscribed neurodermite. Greenhouse thought the disease was that described by Lieberthal and that, though it was clinically like hypertrophic lichen planus, it was actually not lichen planus. This is somewhat contradictory, for Lieberthal's case

12. Fisher, J. E.: Lichen Planus Ocreaformis, Arch. Dermat. & Syph. **26**:586 (Sept.) 1932.

13. Sweitzer, S. E.: Lichen Planus Ocreaformis, Arch. Dermat. & Syph. **26**:1131 (Dec.) 1932.

14. Greenhouse, C. A.: Lichen Planus Ocreaformis, Arch. Dermat. & Syph. **32**:513 (Sept.) 1935.

was in all probability one of lichen planus. Greenhouse [15] has recently stated that subsequent investigation showed the presence of amyloid.

Here again we see that it is unwise to interpolate the word "planus" into the term "lichen ocreaformis" when the ocreaform disease is not lichen planus. This case demonstrates that in all such cases studies for amyloid must be done as the clinical appearance of "lichen obtusus" may be indistinguishable from lichen amyloidosus.[16]

4. Ebert [17] presented a case for Ormsby, under the name "lichen corneus hypertrophicus," which illustrates the utter confusion among highly competent and authoritative dermatologists with reference to this group of diseases.

A man, aged 72, had a rash on the legs of four years' duration. He had from ankles to knees discrete, flat-topped, skin-colored, pinhead-to-bean-sized papules, and also some excoriated papules on the forearms. Histologic examination showed no amyloid. The picture was not that of lichen planus. Though some discussers stated that there were features of prurigo nodularis in the sections, it would be hard to recognize them from the description given. There were hyperkeratosis, acanthosis, elongated papillae, and a perivascular round-cell infiltrate. The heavy cellular reaction in the upper cutis, characteristic of prurigo nodularis, was not present. The features, we think, fitted in eminently well with "lichen obtusus" or "lichen corneus hypertrophicus" of Pautrier. Pusey made a diagnosis of "lichen obtusus corneus," that is, prurigo nodularis. Lieberthal suggested "lichen obtusus." It is difficult to understand exactly what he meant by this term; he surely did not think it was similar to his own "lichen planus ocreaformis" without mentioning it, although it is possible that the case was one of our "lichen obtusus" but not so advanced as to be labeled "ocreaform." He went on to say, as if in contrast to the opinion he had first expressed, that the section suggested prurigo nodularis (which is "lichen obtusus corneus," and to him, and rightly, not identical with "lichen obtusus"). What, therefore, the term "lichen obtusus" conveyed to him is not clear. Schmidt admitted confusion but thought there were features of lichen planus. Ebert indicated that it is important to exclude amyloid by appropriate staining, and that "lichen obtusus corneus" is a synonym of prurigo nodularis. According to him, some of the sections had features of prurigo nodularis, but the clinical appearance excluded this diagnosis in his opinion; the sections showed no evidence of lichen planus, and, though "lichen corneus hypertrophicus" may be associated with lichen planus in the same patient, they are two separate conditions. Pusey finally refused to be moved from his diagnosis of "lichen obtusus corneus" (prurigo nodularis) and refused to recognize the term "lichen corneus hypertrophicus," because, as he said, the case had nothing to do with neurodermite.

We have here a basic difference of opinion of diagnosis. If this was a case of prurigo nodularis, it was not "lichen corneus hypertrophicus," and vice versa. The relation of prurigo nodularis to neurodermite was denied by Pusey, in contrast to

15. Greenhouse, C. A.: Personal communication to the authors.

16. Canada balsam quickly destroys the metachromatic staining of amyloid, which may therefore be overlooked although actually present. Sections should be mounted in "abopon" (a sodium borophosphate, according to the manufacturers, Glyco Products Company, Inc., Brooklyn), and the Nomland test for local staining of amyloid by Congo red should be performed. Unfortunately Congo red is no longer available.

17. Ebert, M. H., for Ormsby, O. S.: Lichen Corneus Hypertrophicus, Arch. Dermat. & Syph. **35**:330 (Feb.) 1937.

the opinion of Pautrier, which we shall discuss later, who regards both prurigo nodularis and "lichen corneus hypertrophicus" as forms of abnormal lichenification, the two being allied but different conditions. However, if Ebert's diagnosis was correct, this was not a case of prurigo nodularis, and he had therefore presented a case of "lichen corneus hypertrophicus" (Pautrier), "lichen obtusus" (Darier), or a less-advanced form of "lichen ocreaformis"—except that Lieberthal himself did not mention this in discussion.

5. Heisel and Krause [18] presented a case as "amyloidosis cutis? lichen planus ocreaformis (Lieberthal)?" in a white man, aged 53, who had a rash of one and one-half years' duration. On the legs, extensor surfaces of the thighs, and the right lower quadrant of the abdomen there were brown-to-violaceous, discrete, round, firm, umbilicated papules with gray scales. On the tibias the lesions formed a mosaic. Histologically, there was no evidence of amyloid, but the features were consistent with lichen planus.

Barney and Gibans found typical lesions of lichen planus on other parts of the body. Arday suggested the diagnosis of keratosis follicularis. Fisher favored the diagnosis of amyloidosis cutis, in spite of lack of histologic evidence of amyloid. Netherton agreed with Fisher but said that the case presented was identical with another case of his, which he said, was one of lichen planus ocreaformis. He must, therefore, have been of the opinion that Lieberthal's case was one of lichen amyloidosus. Cole diagnosed the case as an instance of lichen planus, and seems to have been correct, on account of the many clinical features, as well as the histologic picture, which were consistent with lichen planus, and he stated that in view of the clinical appearance he thought it was lichen planus ocreaformis of Lieberthal.

6. Sweitzer [19] showed a case of "lichen planus ocreaformis," in a white man, aged 87, who showed progression of lesions for eight years. Scattered on the legs from ankles to knees he had purplish-brown, painless, sharply circumscribed, indurated, slightly elevated, dry papules, with some adherent scales. A biopsy specimen showed no evidence of lichen planus, and no mention was made of examination for amyloid.

Michelson had veered from his views of 1932, and stated that he was not sure of the meaning of "ocreaformis," and was not prepared to make a diagnosis. Montgomery thought the case might have been one of Blum's purpuric pigmented lichenoid dermatitis, thus introducing yet another complicating factor into the differential diagnosis. This case might well have been one of "lichen (not planus) ocreaformis," or of amyloidosis.

7. Obermayer [20] presented a case of "lichen ruber moniliformis" in a white woman, aged 45, with an eruption of over 20 years' duration. From ankles to knees she had flat, slightly erythematous, waxy, densely set papules 2 to 4 mm. in diameter, of firm consistency, forming plaques in some areas, and in bead-like arrangement in others. It was conceded by those at the meeting at which this case was presented that there was a superadded radiodermatitis. A biopsy specimen showed no evidence of lichen planus or of amyloid, but there were hyperkeratosis, hypergranulosis, mild acanthosis, and signs of radiodermatitis.

18. Heisel, E. B., and Krause, M. E.: A Case for Diagnosis (Amyloidosis Cutis? Lichen Planus Ocreaformis [Lieberthal]?), Arch. Dermat. & Syph. **45**:607 (March) 1942.

19. Sweitzer, S. E.: Lichen Planus Ocreaformis, Arch. Dermat. & Syph. **49**:450 (June) 1944.

20. Obermayer, M. E.: A Case for Diagnosis: Lichen Ruber Moniliformis (?), Dermatitis Actinica from Roentgen Ray Therapy of Legs, Arch. Dermat. & Syph. **56**:404 (Sept.) 1947.

Goeckerman thought the condition was not lichen planus, but was more closely related to neurodermatitis. He would best apply the term "lichen ocreaformis" to the disease, which, he said, was in some cases associated with recollections by the patients "of sexual experiences of a profoundly abnormal character." We have here, for the first time, a clear and incisive use of the term "lichen ocreaformis" without the "planus" interpolated, and the relationship to neurodermatitis is again suggested. Obermayer considered two possibilities: (*a*) lichen amyloidosus, which was here excluded by suitable staining—he also pointed out the pitfalls in the histologic search for amyloid—and (*b*) lichen ruber moniliformis, which he said may simulate the papular form of neurodermatitis.

This moniliform dermatosis was probably an example of the disease we are discussing, but it was not "lichen ruber moniliformis." If by the latter term Obermayer was referring to the disease described and named "lichen ruber monileformis" by Kaposi,[21] and later called "morbus moniliformis lichenoides" by Wise and Rein,[6] then it must be pointed out that there was no resemblance between this case and those of Kaposi or Wise and Rein; nor could he have meant a moniliform type of true lichen (ruber) planus, because the histologic features were not those of lichen planus.

8. Rothman[22] presented a case of "lichen obtusus? prurigo nodularis?" in a white man, aged 25, who had an eruption of 12 years' duration on the medial malleoli. He had hard, round, semiglobular, elevated, finely scaling, bean-sized papules, partly confluent, partly in linear arrangement. The condition had been apparently cured for three years by x-rays and tars, but it recurred and had been present for three years before the meeting at which his case was reported. Sections were histologically interpreted as prurigo nodularis, there being no features of lichen planus.

The discussers were of the opinion that search for amyloid should have been made, though the fact that the patient was well for three years made it unlikely that amyloid would have been found. The clinical similarity of the dermatosis to hypertrophic lichen planus was noted, and Becker thought the case was one of hyperkeratotic neurodermatitis.

Again the similarity to amyloidosis and the importance of excluding it by methods fortunately at our disposal is mentioned. Histologic examination ruled out lichen planus. The photograph was not that of prurigo nodularis (lichen obtusus corneus). Rothman's diagnosis of "lichen obtusus" in Darier's sense of the term was, therefore, the most probable. Becker's view of the condition as a hyperkeratotic neurodermatitis approaches Pautrier's opinion of the etiologic relationship between "lichen obtusus" ("lichen corneus hypertrophicus") on the one hand, and prurigo nodularis ("lichen obtusus corneus", "chronic nodular circumscribed lichenification") on the other.

9. Bechet[23] presented a case of "lichen planus ocreaformis (Lieberthal)" in a white man, aged 73, who had a rash below the knees of some 10 years' duration.

21. This is Kaposi's original spelling. The accepted American form is moniliformis. Kaposi, M.: Lichen ruber monileformis, Vrtljschr. Dermat. **13**:571 and plates 19, 20, and 21, 1886.

22. Rothman, S.: A Case for Diagnosis (Lichen Obtusus? Prurigo Nodularis?), Arch. Dermat. & Syph. **57**:477 (March, Pt. 2) 1948.

23. Bechet, P. E.: Lichen Planus Ocreaformis (Lieberthal), Arch. Dermat. & Syph. **57**:496 (March, Pt. 2) 1948.

He had had an eruption on the arms which had disappeared. The lesions on the legs consisted of many rounded, dome-like, hyperkeratotic, bronish papules covering the greater part of the lower third of the legs; there was no confluence of lesions. Bechet drew attention to the resemblance between his case and the picture of lichen planus ocreaformis in Suttons' textbook.

As no histologic report was given, no adequate analysis can be made in the case. Lichen planus was suggested as a possible diagnosis, as well as "lichen moniliformis," whatever might have been meant by that term.

CLASSIFICATION AND DISCUSSION OF TYPES

The "ocreaform" conditions discussed must, in the light of later analysis, be regarded as a composite of various diseases, so that the cases were of three types:

1. Ocreaform varieties of true lichen planus are the first type, and only these cases warrant the name "lichen planus ocreaformis."

2. The second type is lichen amyloidosus, which was beginning to be described and well-recognized in 1929 to 1930 in the publication of Freudenthal, Gutmann, and Koenigstein.[24] Cases in the United States prior to this period were obviously not investigated for amyloid. Search for it must be made in all cases; and if found, whatever the form of the lesions, the condition should be called amyloidosis, not "lichen planus ocreaformis," for this misses the most important point of the amyloid nature of the disease, while stressing the relatively unimportant element of its "ocreaformity," and is further in error in labeling the condition as a lichen planus, which it is not.

3. The third type includes cases which are neither of the first two types but which are perhaps related to abnormal forms of response to scratching and rubbing as a result of severe pruritus. These are the "lichen obtusus" of Darier and the "lichen corneus hypertrophicus" of Pautrier. If Lieberthal's vivid term is to be used for some of these cases, because of the clinical appearance, then the condition should be called "lichen ocreaformis" without the "planus."

Lesions arranged in plaques or rows of beads, referred to as ocreaform or moniliform, are similar, and these adjectives have, as a result, been loosely and indiscriminately used as descriptive terms which have led to diagnostic errors.

Kaposi's case of lichen ruber monileformis[21] showed a fantastic clinical picture which was neither that of lichen ruber (planus) nor that of the "ocreaform" condition described in the cases cited. In it there was a widespread, symmetrical, almost keloid-like eruption, which on the thighs formed bizarre geometric figures. Histologically, the features as seen in the original plates are not those of lichen planus. The rete pegs were well formed, and the basal layer was intact. A band of normal collagen separated the epidermis from a massive infiltrate, occupying the larger part of the cutis, which was composed of whorls of spindle-shaped cells within which there were many multinucleate giant cells. Small round cells were significantly absent. Though Miller[25] presented a case of "lichen verrucosus et

24. Freudenthal, W.; Gutmann, C., and Koenigstein, H., cited by Michelson, H. E., and Lynch, F. W.: Systematized Amyloidosis of the Skin and Muscles, Arch. Dermat. & Syph. **29**:806 (June) 1934.

25. Miller, H. E.: Lichen Verrucosus et Reticularis (Kaposi); Porokeratosis Striata (Nékàm); Morbus Moniliformis Lichenoides (Wise and Rein), Arch. Dermat. & Syph. **52**:129 (Aug.) 1945.

reticularis (Kaposi); porokeratosis striata (Nékám); morbus moniliformis lichenoides (Wise and Rein)," in which some of the lesions had the histologic features of lichen planus, the clinical and histologic findings in Kaposi's own case of "lichen ruber monileformis" were such as to differentiate it clearly from lichen planus, as well as from the "ocreaform" conditions we are considering here.

VIEWS OF THE FRENCH SCHOOL

"Lichen obtusus corneus" (prurigo nodularis) should not be confused with "lichen obtusus" (Darier), which is a term used for some conditions with "ocreaform" or "obtuse" lesions that are clinically very different from prurigo nodularis, i. e., those cases which are neither lichen planus nor amyloidosis, and which admittedly may be called "lichen ocreaformis" (without the interpolation of "planus").[26] Unless etiologic unity is found between lichen obtusus corneus (prurigo nodularis) and lichen obtusus (lichen ocreaformis), the two sets of terms ought not to be used interchangeably; and even if such etiologic relationship were established, it might still be very worth while to distinguish between the two in nomenclature on account of the great clinical dissimilarity of the two conditions.

Pautrier's findings, moreover, of increased vascularity and neuroma-like formation in prurigo nodularis (which he has so far found in no other inflammatory condition) would speak strongly against a monistic attitude, in spite of the fact that he is of the opinion [27] that "lichen obtusus corneus" (prurigo nodularis) and "lichen corneus hypertrophicus" (the condition herein discussed) are both types of abnormal lichenification, and that they are due to repeated trauma in persons particularly disposed to have such skin responses.

In Pautrier's "circumscribed chronic nodular lichenification" (lichen obtusus corneus, prurigo nodularis) there are important histologic findings. The surface is wavy; there is hyperkeratosis and plugging, a stratum lucidum, and the granular layer is six to 10 cells thick. Sometimes compact areas of parakeratosis are found within the horny layer. Acanthosis is mild, and the basal layer is intact. With Masson's trichrome stain there are collections of bands of infiltrate in the upper or midcutis, composed of lymphocytes and histiocytes, some plasmacytes, eosinophiles, and neutrophiles. The connective tissue is seen as a fine reticulum in the affected area, while at the periphery it is sclerotic. The elastica is destroyed. The vessels are increased in number, their endothelium is swollen and the lumens dilated. More characteristic, however, than these is the presence within, at the margins of, or surrounding the infiltrate of nerve bundles which belong to the cerebrospinal system and which may terminate in the epidermis. This is apparently a true neuroma formation which is found in no other inflammatory condition as the objective cause of pruritus.

Pautrier states that lichen obtusus corneus (prurigo nodularis) has often been mistakenly considered and described as a variety of lichen planus. It bears no resemblance to "lichen obtusus" of Unna, which we shall discuss later, other than

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26. Andrews, G. C.: Diseases of the Skin, ed. 3, Philadelphia, W. B. Saunders Company, 1946, p. 87. Andrews gives not only "lichen obtusus corneus" as a synonym for prurigo nodularis but also "lichen corneus hypertrophicus," a term introduced by Pautrier for our condition which is not prurigo nodularis, though as explained above, there may be etiologic relationship between the two.

27. Pautrier, L. M.: Les lichénifications, in Nouvelle pratique dermatologique, edited by J. Darier, Paris, Masson & Cie, 1936, Vol. 7, pp. 494-495, 497-500, 521-535, 544-559.

similarity of name. The term "lichen ruber verrucosus," which has at times been erroneously applied to it, should be limited to cases of true lichen planus which are verrucous. No primary lesions of lichen planus are found; no mucous membrane lesions are seen; pruritus precedes the appearance of the lesion and is much worse than in lichen planus; the infiltrate does not hug the epidermis, nor does the epidermis show the features of lichen planus, while the vascularity and the neuroma formation are distinctive.

It is an abnormal lichenification and therefore best called "circumscribed chronic nodular lichenification," not "prurigo nodularis," as it has nothing to do with the prurigos of Hebra or with chronic urticaria, which, therefore, should at all events not be included in the terminology of the disease.

Pautrier prefers the term "lichen corneus hypertrophicus" for verrucous lichenification, which has been described under various names, such as "lichen planus corneus et hypertrophicus," "lichen corneus verrucosus," "lichen corneus," "circumscribed hypertrophic dermatitis." It is seen on the extensor aspects of the legs, thighs, perianal area, and rarely on the arms. It consists of regular, pink-to-brownish papules, sometimes forming plaques, covered with horny or very adherent scales, and is intensely pruritic.

Though these lesions may be associated with or intermingled with lesions of true lichen planus, Pautrier has found that in 50% of cases there is no coincident lichen planus. He therefore cannot agree that these papules are a variety of lichen planus, or that they are an end-result of this disease leaving no evidence of true lichen planus.

Histologically, when both kinds of lesions are present, those which are not lichen planus show a normal granular layer, good columnar basal cells, and no "washing-out" of the margin. A lymphocytic and plasmacytic infiltrate is separated from the epidermis by a band of normal collagen; the papillae are edematous and their vessels dilated.

In pure cases, without lichen planus, there is hyperkeratosis, a thick but regular granular layer, and thick acanthotic rete pegs which are not obliterated as in lichen planus, and the basal layer is well defined. In the cutis there is increased vascularity and a scattered banal cellular reaction. Thus the resemblance to common lichenification is great, while there is no lichen-planus picture.

The mixed cases are interpreted by Pautrier as being lichen planus, which, because of its pruritic nature, is accompanied by a secondarily produced and abnormal lichenification, which manifests itself as "lichen corneus hypertrophicus," just as lichen planus may in other and more frequent cases be accompanied by "normal" lichenification as a result of rubbing. However, the fact that in many cases the lesions are purely those of "lichen corneus hypertrophicus" without any lichen planus lesions, shows that the two lesions are not those of one and the same disease, and that it is a particular and "verrucous" kind of lichenification which may be superimposed upon various dermatoses, such as lichen planus, eczema, prurigo.

VIEWS OF THE GERMAN SCHOOL

According to Juliusberg,[28] obtuse papular lesions were described by Unna, occurring as the lesion of lichen ruber planus together with more characteristic

28. Juliusberg, F.: ruber und Pityriasis rubra pilaris, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1931, Vol. 7 (Pt. 2) p. 17.

papules, or even being the preponderant lesion. It was found more commonly in children, and apparently was an unusual type of primary lesion of true lichen planus. Obtuse papular lesions can, however, be found in other conditions, and the finding of obtuse papules in lichen obtusus corneus (prurigo nodularis), as well as in lichen ruber (planus), has mistakenly led some authors to relate the former to the lichen planus group.

Hypertrophic and verrucous lichen planus of the shins may take on various forms. Sometimes there are hemispherical lesions, differing only slightly in color from the surrounding skin, the configuration of which is reminiscent of the form of papule for which Unna proposed the term "obtusus." The papules may be thickly set to cover large areas of skin, while separate from these plaques and beyond their margins isolated papules with the same features may be seen. The papules may resemble the individual lesions of lichen obtusus corneus (prurigo nodularis), a condition which, on account of the isolated nature of the lesions alone, is different from the obtuse verrucous form of lichen planus. It is at times difficult to differentiate this type of lichen planus verrucosus from the obtuse papules of certain forms of circumscribed neurodermatitis. But in most cases of lichen planus verrucosus the lesions have a different character: They are more oval, though they may also form irregularly outlined plaques; they are sometimes over varicose veins, and they have a brown-red or blue-red color and a definitely warty surface in which there are many depressions giving it a sieve-like or honeycombed appearance. Some authors would include these cases of obtuse and verrucous lichen planus in the neurodermatitides; but in a number of cases the presence of typical lichen-planus papules in the vicinity, or on other parts of the body, establish the lichen-planus nature of these lesions. This fact can easily be confirmed by histological examination, because the obtuse forms of lichen planus show but minor deviations from the classic histologic picture of lichen planus.

Eruptions called "lichen obtusus," definitely variants of lichen planus, in which all the lesions are obtuse papules, or in which the presence of obtuse papules is an outstanding feature coexistent with ordinary lichen-planus papules, have been described by Büeler on the axilla, and by Habermann on the supraclavicular areas. Büeler called them "lichen obtusus," though he regarded them as variants of lichen planus, while Habermann would rightly not refer to them as "lichen obtusus," which is a term that lacks the lichen ruber (planus) factor and, moreover, leads to confusion with the unrelated "lichen obtusus corneus," which is prurigo nodularis. Gans regards "lichen obtusus" of Unna as a variant of true lichen planus.

Pictures and descriptions of prurigo nodularis have erroneously found their way into textbooks under the title of "lichen obtusus" and in the chapters on lichen planus. However, M. Winkler [29] writes that prurigo nodularis may be mistaken clinically for "lichen obtusus" of Unna unless confirmed by histologic examination or by the concomitant presence of typical lichen planus lesions. It is clinically very different from chronic neurodermatitis, though they may be etiologically related, as is the opinion of Pautrier, who called prurigo nodularis "chronic nodular circumscribed lichenification."

29. Winkler, M.: Prurigo, Strophulus, Pruritus, in Jadssohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1929, Vol. 6 (Pt. 1) p. 322.

Alexander,[30] in his discussion of atypical forms of circumscribed neurodermatitis, is inclined to agree with Pautrier, though he is somewhat reserved and qualifying in his concurrence. He does not mention "lichen corneus hypertrophicus" as being one of the variants and atypical forms of circumscribed neurodermatitis as does Pautrier, nor does he differentiate it from prurigo nodularis, though many of the cases he cites under a host of different names given by the presenters of individual cases are clearly not cases of prurigo nodularis, but are cases of, or closely allied and similar to, "lichen corneus hypertrophicus."

In their article on seborrheic dermatitis, F. Winkler and Unna [31] have a colored reproduction which is a fair example of "lichen corneus hypertrophicus," but which, on account of Unna's determined concept of lichenification as a variant of eczema, is called "eczema verruco-callosum."

CONCLUSIONS

Out of this maze of names and opinions we feel it will best serve to clarify the situation if we adopt for the condition in point Pautrier's nomenclature of "lichen corneus hypertrophicus" for the following reasons:

1. To avoid the concept of lichen planus which is contained in the terms "lichen planus ocreaformis" and "lichen planus obtusus" for conditions which are not lichen planus;

2. To avoid the term "lichen ruber moniliformis," a name attached to a disease which is neither lichen (ruber) planus nor the "ocreaform," at times "moniliform," condition which we are here discussing;

3. To avoid confusion between "lichen obtusus corneus" (prurigo nodularis) and "lichen obtusus" which is one of the terms that has been applied to the condition we are here attempting to analyze;

4. To avoid the term "ocreaformis" which, though picturesque, would apply only to advanced cases in which there are features of an "ocrea," greave, or legging, and thus allowing for the less-advanced types which are more commonly seen, and

5. To avoid the association of the ideas "ocreaform" and "moniliform" which has proved so unnecessarily confusing.

In addition, finally, Pautrier's term takes cognizance of the whole problem of abnormal, individualistic response of the skin to chronic and repeated trauma by "grattage," and also allows for the relationship of the condition to lichen chronicus simplex, while at the same time recognizing the interesting and unusual clinical lesions.

SUMMARY OF NOMENCLATIVE AND NOSOLOGIC POINTS

1. Acne Urticatus (Kaposi).—As a synonym for prurigo nodularis this term should be discarded. Its use for other conditions is of debatable wisdom.

2. Amyloidosis (Lichen Amyloidosus).—This term should be used for amyloid deposits in the skin whatever the clinical appearance of the lesions, on account of the over-all importance of the presence of amyloid.

3. Chronic Nodular Circumscribed Lichenification (Pautrier).—This is a synonym for prurigo nodularis.

4. Eczema Verruco-Callosum (Unna).—This term probably refers to the disease discussed.

30. Alexander, A.: Neurodermatitis, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1929, Vol. 6 (Pt. 1) p. 387.

31. Winkler, F., and Unna, P. G.: Das seborrhoische Eczem, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1929, Vol. 6 (Pt. 1) p. 476.

5. Lichen Corneus Hypertrophicus (Pautrier).—This in our opinion is the most acceptable term for the disease discussed. This is not prurigo nodularis.

6. Lichen Moniliformis.—As a synonym for the disease discussed this term should be discarded, on account of confusion with the disease described by Kaposi (15 and 16) which is entirely different.

7. Lichen Obtusus (Darier)—This term refers to the disease discussed. It is better discarded on account of confusion with "lichen obtusus" of Unna (8).

8. Lichen Obtusus (Unna).—This is an "obtuse" form of true lichen ruber (planus) and should, therefore, be called "lichen ruber obtusus" (7). It would be contradictory to use the accepted American terminology and say "lichen planus obtusus."

9. Lichen Obtusus Corneus (Brocq).—This is an accepted synonym for prurigo nodularis.

10. Lichen Ocreaformis.—By use of this term reference is made to an "ocreaform" papular disease here discussed, which is neither lichen planus nor amyloidosis but which is probably a form of lichenification and thus related to circumscribed neurodermatitis.

11. Lichen Planus.—Alone or with adjectives added, this term should be used only for types of true lichen (ruber) planus.

12. Lichen Planus Ocreaformis (Lieberthal).—This is an "ocreaform" type of true lichen planus.

13. Lichen Polymorphe Ferox (Vidal).—This term is a synonym for prurigo nodularis and should be discarded on account of confusion with prurigo ferox of Hebra.

14. Lichen Ruber.—Alone or with qualifying adjectives, this term should be used only for types of true lichen ruber (planus), except, however, that it is accepted usage to refer to "lichen ruber acuminatus," the relation of which to lichen ruber (planus) as well as to pityriasis rubra pilaris is a matter of controversy.

15. Lichen Ruber Monileformis (Kaposi) or Lichen Ruber Moniliformis (American usage).—This disease is not lichen ruber (planus), and the term had better be discarded. It is moreover very different from the disease discussed. Kaposi's term, if used at all, might be reserved for a moniliform type of true lichen ruber (planus); but as his term is used for the disease he described, unnecessary confusion would result. (6 and 16).

16. Morbus Moniliformis Lichenoides (Wise and Rein).—This is a preferable term for "lichen ruber monileformis" of Kaposi (6 and 15).

17. Prurigo Nodularis (Hyde).—This disease should not be confused with prurigo of Hebra.

18. Urticaria Chronica Papulosa (Fabry).

19. Urticaria Perstans Papulosa (Kreibich).

20. Urticaria Perstans Verrucosa (Baker).—These three terms should be discarded as unnecessary synonyms for prurigo nodularis.

2 W. 87th St. (24).
117 Midwood St. (25).

ANTIBIOTIC SENSITIVITY AND MONILIASIS

A. J. REICHES, M.D.
ST. LOUIS

AT THE present time there is clinical evidence to show that sensitivity to various antibiotics may be a factor in the development of clinical moniliasis during and following antibiotic therapy. Parets,[1] and Peck and Feldman [2] have described sensitivity to antibiotics. Harris,[3] and Wood, Manning Jr., and Patterson [4] have reported monilial invasion of the mucous membrane of the oropharynx and the gastrointestinal and pulmonary tracts. It is felt that pulmonary moniliasis developing during antibiotic therapy is usually secondary to moniliasis of the oropharynx.

I wish to make note of the frequent monilial involvement of the genitocrural area during and after antibiotic therapy. Such involvement has been confirmed by smears from the genitocrural dermatitis.

Antibiotics, such as aureomycin, chloramphenicol, and terramycin, apparently interfere with the various factors which limit the growth of Candida albicans. It is, however, quite unusual for Candida (Monilia), not generally a primary invader, to give symptoms without actually invading tissue.

The genitocrural dermatoses herein reported represent one phase of a side reaction from antibiotics, which permits us to visualize the following processes. It is felt that sensitization to antibiotics has decreased tissue resistance to the Candida. One possibility which has been considered is the acceleration of monilial growth by antibiotics. Wood, Manning Jr., and Patterson [4] have found that antibiotics have no effect on Candida in vitro. Moore,[5] however, has shown that aureomycin hydrochloride does stimulate the in vitro growth of C. albicans.

REPORT OF CASES

Genitocrural dermatitis due to Candida follows the use of antibiotics quite often in my experience. Patients have been observed who, having taken antibiotics for more than one course, have developed a genitocrural dermatitis during or after

1. Parets, A. D.: Angioneurotic Edema and Rash Due to Aureomycin, J. A. M. A. **143**:653-654 (June 17) 1950.

2. Peck, S. M., and Feldman, F. F.: Sensitivity Reaction to Aureomycin, J. A. M. A. **142**:1137-1139 (April 5) 1950.

3. Harris, J. H.: Aureomycin and Chloramphenicol, J. A. M. A. **142**:161-164 (Jan. 21) 1950.

4. Wood, J. W.; Manning, Jr., and Patterson, C. N.: Monilial Infections Complicating Therapeutic Use of Antibiotics, J. A. M. A. **145**:207-211 (Jan. 27) 1951.

5. Moore, M.: In Vivo and in Vitro Effect of Aureomycin Hydrochloride on Syringospora (Monilia, Candida Albicans), J. Lab. & Clin. Med. **37**:703-712 (May)1951.

each course. There was also one patient sensitized to chloramphenicol on whom were observed the effects of the antibiotic directly applied to the perianal skin. The monilial overgrowth was demonstrated by methylene-blue-stained smears.

A. W., a 41-year-old white man who had a severe cold, was taking 250 mg. of chloramphenicol every six hours. A dermatitis developed with severe anal burning and itching on the pubic, perianal, and anal regions. An antihistamine ointment used locally gave complete relief. Three weeks after the original dermatitis had subsided a chloramphenicol ointment was prepared and applied to the perianal regions of this patient. Within one and one-half hours after the application of the ointment the patient developed intense burning and itching sensations. Local therapy with antihistamine ointment gave immediate relief.

S. W., a 46-year-old white woman with multiple boils was given 250 mg. of terramycin every six hours. After the ninth dose diarrhea developed, with anal and perianal itching, burning, and a vulvovaginitis. Local therapy with antihistamine ointment gave immediate relief. The terramycin was continued, and the dermatitis cleared up at the end of about two days. Terramycin was again administered approximately two weeks later, and again itching and burning of the anal, perianal and vulvar regions developed. The antihistamine ointment was used, and the patient was able to continue the use of terramycin.

P. W., a 53-year-old white man had a virus infection and took 500 mg. of aureomycin. On the ninth dose a perianal burning, itching, and inflammation of the skin began to develop. Antihistamine ointment was applied and the patient continued with aureomycin therapy. Three months later this man again took aureomycin for a nasopharyngeal infection and again a genitocrural dermatitis developed after the eighth dose.

Diarrhea is not an essential factor in causing the pruritus. Reiches and Webb [6] in reporting 13 cases of genitocrural pruritus from aureomycin noted that diarrhea developed in only eight of the cases.

COMMENT

Harris [3] has shown and stated that Candida does grow and perhaps gain virulence following the destruction of intestinal bacteria by the oral use of antibiotics. He also felt that the resistance of tissue may have been lowered by the effect of riboflavin or vitamin-B deficiency.

However, I feel that the sensitivity to the antibiotics, which in the above-reported cases was a predominantly perianal sensitivity, is a factor in causing the genitocrural pruritus. Some of these patients had no apparent anal or perianal dermatitis, yet they had symptoms of itching and burning during and immediately after antibiotic therapy. In other cases observed, the reaction started with a burning and itching with no apparent signs, but within 24 to 36 hours typical monilial invasion and dermatitis of the skin developed, as proved by microscopic examinations. I do not feel that the Candida, which can be observed by methylene blue smears and by culture, will ordinarily bring about symptoms without actual invasion of the skin. Patients who have experienced burning, itching and dermatitis may manifest the same syndrome again on taking the same antibiotic (Cases 2 and 3). Shelmire [7] has shown a similar reaction following oral ingestion of poison ivy oleoresin.

Patients who are sensitive to penicillin can be given aureomycin, terramycin, or chloramphenicol without any signs of allergic reaction. Apparently there is a

6. Reiches, A. J., and Webb, P. K.: Genito-Crural Pruritus from Oral Aureomycin. A. M. A. Arch. Dermat. & Syph. **64**:63-64 (July) 1951.

7. Shelmire, B.: Hyposensation of Poison Ivy, Arch. Dermat. & Syph. **44**:983-998 (Dec.) 1941.

specific sensitivity to each of these antibiotics. Two patients were observed in whom a genitocrural dermatitis developed due to aureomycin therapy but who took terramycin without the development of the syndrome.

It is possible that the effect of antibiotics on intestinal flora will decrease vitamin-B-complex synthesis of intestinal bacteria and may be a factor in continuing the monilial phase of this dermatitis.

Phenindamine phosphate (thephorin®) ointment, which has a marked anesthetic and soothing effect, was applied to the genitocrural area with good results. However, some patients have exhibited a marked sensitivity to phenindamine; so it must be used with caution. Similar antihistamine ointments are as satisfactory.

SUMMARY

Monilial invasion subsequent to antibiotic therapy seems likely to be a sequela to the tissue changes produced by the sensitization reaction.

4500 Olive St.

PODOPHYLLOTOXIN TREATMENT OF MICROSPORUM AUDOUINI SCALP INFECTIONS

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THE CLINICAL importance of podophyllotoxin [1] has been an outgrowth of extensive use of podophyllin (podophyllum resin) within recent years. Kaplan [2] in 1942 reported the topical application of podophyllin, the resin obtained from the root of Podophyllum peltatum, to be effective against condyloma acuminatum. Topical use of podophyllin has been found of value also in granuloma inguinale,[3] basal-cell carcinoma,[4] and scalp infections due to Microsporum lanosum and M. audouini.[5] Podophyllin inhibits mitosis and acts as a direct cellular toxin.[6]

Sullivan,[7] using chemical, biologic, and pathologic methods, found podophyllotoxin to be the active principle of podophyllin. Podophyllotoxin is a complex tricyclic substance with the formula $C_{22}H_{22}O_8$, and may be inactivated by alkaline hydrolysis in both aqueous and alcoholic solutions. It inhibits the cellular respiration, in vitro, of rat lymph nodes, thymus, kidney tumor, spleen, liver, brain, and testis.[8] The podophyllotoxin content of commercial podophyllin resin varies from 28 to 52%.[9] Because of this variance I believe that future investigators with podophyllin compounds should utilize assayed samples or crystalline podophyllotoxin.

It is the purpose of this paper to report the in vitro and in vivo effects of crystalline podophyllotoxin on M. audouini.

From the Department of Dermatology and Syphilology, University of Virginia School of Medicine and Hospital.

1. The podophyllotoxin was furnished by Dr. W. G. Bywater of S. B. Penick & Company.

2. Kaplan, I. W., cited by King, L. S., and Sullivan, M.: Effects of Podophyllin and of Colchicine on Normal Skin, on Condyloma Acuminatum and on Verruca Vulgaris: Pathological Observations, Arch. Path. **43**:374 (April) 1947.

3. Tomskey, G. C.; Vickery, G. W., and Getzoff, P. L.: The Successful Treatment of Granuloma Inguinale, with Special Reference to the Use of Podophyllin, J. Urol. **48**:401, 1942.

4. Sullivan, M.: Treatment of Cutaneous Carcinoma with Podophyllin, Bull. Johns Hopkins Hosp. **85**:200, 1949.

5. Reiss, F.: The Effect of Podophyllin on Pathogenic Fungi and Its Clinical Application in Treatment of Tinea Capitis, Exper. Med. & Surg. **7**:229, 1949.

6. Belkin, M.: Effect of Podophyllin on Transplanted Mouse Tumors, J. Pharmacol & Exper. Therap. **93**:18, 1948.

7. Sullivan, M.: Podophyllotoxin, Arch. Dermat. & Syph. **60**:1 (July) 1949.

8. Miller, Z. B.; Davison, C., and Smith, P. K.: The Effect of Podophyllotoxin on Tissue Metabolism and Enzyme Systems, J. Exper. Med. **90**:525, 1949.

9. Warren, L. E.: Assay of Resin of Podophyllum, J. A. Official Agric. Chemists **13**:117, 1930.

IN VITRO EFFECTS

Material and Procedure.—To determine the inhibitory effect of crystalline podophyllotoxin on M. audouini, infected hairs were placed in 1 and 3.3% solutions in 90% alcohol. Hairs were

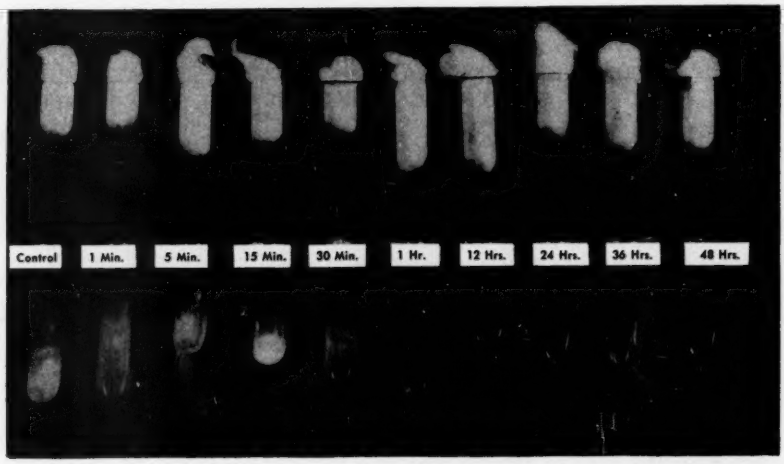

Fig. 1.—Inhibition of M. audouini after 60-minute contact with 1% podophyllotoxin.

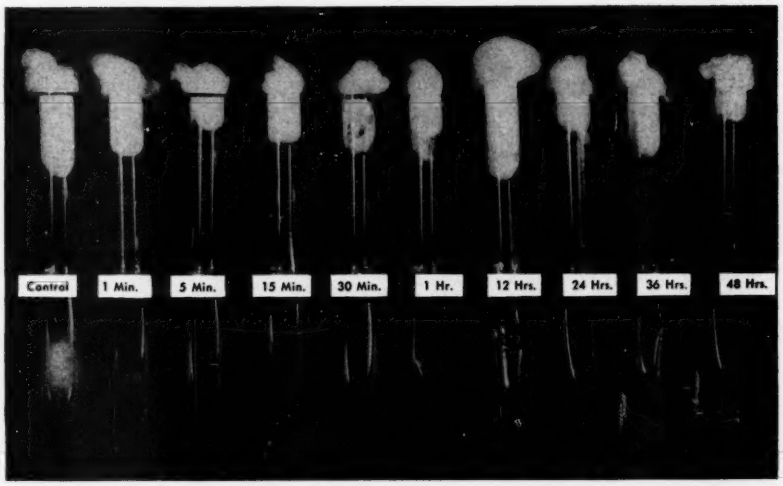

Fig. 2.—Inhibition of M. audouini after one-minute contact with 3.3% podophyllotoxin.

left in the podophyllotoxin solutions for 1, 5, 15, 30, and 60 minutes, and for 12, 24, 36, and 48 hours, respectively. They were then cultured on Sabouraud's dextrose medium at room temperature. Control cultures of untreated hairs and hairs treated in the alcohol vehicle presented normal growth.

Results.—Those hairs which had been in the 1% solution of podophyllotoxin presented retardation of growth after 5 minutes, with advanced inhibition occurring at 30 minutes, and complete cessation of growth at 60 minutes (Fig. 1).

Those hairs which had been exposed to the 3.3% solution presented no growth (Fig. 2).

Culture mounts from the inhibited cultures showed granular changes within the hyphae and a paucity of chlamydospores, racquet mycelium and macroconidia.

IN VIVO EFFECTS

Material and Procedure.—Fourteen patients with M. audouini infections of the scalp were treated. Nine infections were of more than one year's duration and had not improved on four months' treatment with 5% salicylanilide ointment. The remaining infections were of unknown duration but had received no treatment. All patients were Negroes. Reaction to the trichophytin test, using undiluted antigen (Eli Lilly & Company), was negative in every patient.

Treatment consisted of daily applications (excluding Saturdays and Sundays) of 3.3% podophyllotoxin in 90% ethyl alcohol for a period of 30 days. The scalp was massaged well during treatment. Conjunctivitis was avoided by careful application of medication and thorough instructions to the patients. All examinations and treatments were performed by one physician.

Results.—Nine patients (64%) were clinically and mycologically cured in 30 days. Reexaminations at one- and two-month intervals showed no fluorescence under Wood's light, and skin cultures and hair cultures were negative for the fungus. Five cured patients had not improved on prolonged salicylanilide therapy. Cures were observed in patients of all ages between 6 and 12 years. Folliculitis occurred in nine patients on the seventh to the twentieth day of therapy but, upon continued treatment, progressed to form soft encrustations without kerion formation or lymphadenopathy. No scarring was noted. Five cured patients presented cutaneous reactions.

COMMENTS

The cure of 64% of M. audouini infections of the scalp after 30 applications (once daily) indicates the effectiveness of a regimen using topical 3.3% podophyllotoxin in alcohol. Swartz and his co-workers,[10] using salicylanilide ointment, observed an average cure-time of 40 days for 57% of their patients. Carrick[11] found that undecylenate-undecylenic acid ointment and propionate-propionic acid ointment cured 40% of M. audouini scalp infections in an average treatment period of 125 to 132 days, respectively. It should be emphasized that podophyllotoxin therapy was continued during any cutaneous reactions, whereas Swartz and Carrick stopped treatment whenever irritation occurred.

The spontaneous cure of tinea capitis at puberty has been attributed by Rothman and his co-workers[12] to the production of monobasic normal aliphatic acids having an odd number of carbon atoms, with the maximum in vitro effectiveness occurring in that acid containing seven atoms and remaining at this maximum with 9, 11, and 13 carbon-containing acids. Although all our patients were Negro children, none had reached puberty, and cures were distributed over all age groups. The cure rate observed in our group is above the 27% spontaneous cure observed by Livingood and Pillsbury[13] in uncomplicated cases of M. audouini.

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10. Swartz, L.; Peck, S. M.; Botvinick, I.; Armond, L. C., and Frasier, E. S.: Control of Ringworm of Scalp Among School Children in Hagerstown, Md., 1944-1945, J. A. M. A. **132**:58 (Sept. 14) 1946.

11. Carrick, L.: Methods of Local Therapy for Tinea Capitis Due to Microsporon Audouini, J. A. M. A. **131**:118 (Aug. 10) 1946.

12. Rothman, S.; Smiljanic, A. M., and Shapiro, A. L.: Fungistatic Action of Hair Fat on Microsporon Audouini, Proc. Soc. Exper. Biol. & Med. **60**:394, 1945.

13. Livingood, C. S., and Pillsbury, D. M.: Ringworm of the Scalp: Prolonged Observation, Family Investigation, Cultural and Immunological Studies in 130 Cases, J. Invest. Dermat. **4**:43, 1941.

The possibility of direct in vivo fungicidal ability of podophyllotoxin is shown by the four patients who responded to therapy without clinical evidence of folliculitis.

We believe that podophyllotoxin should prove to be a satisfactory adjunct in the treatment of both new and recalcitrant infections with M. audouini. It is advantageous in that it has a definite in vitro and in vivo inhibitory effect on the fungus, frequently produces sufficient follicular reaction to loosen infected hairs, and is simple and safe to use.

It would be desirable to repeat this investigation on a larger series of patients in which suitable control studies could be made.

CONCLUSIONS

Hairs infected with Microsporum audouini, when exposed to a 3.3% alcoholic solution of podophyllotoxin for one minute, show no growth when placed on Sabouraud's dextrose media. When a 1% solution of podophyllotoxin is used, retardation of growth is noted after five minutes' contact and complete cessation of growth occurs after 60 minutes' exposure.

Fourteen patients with M. audouini of the scalp were treated daily for 30 days with topical 3.3% podophyllotoxin in alcohol. Nine patients were clinically and mycologically cured. Five of the cured patients had not responded to four months' treatment with salicylanilide ointment. Folliculitis was frequently noted but was not essential to cures.

Topical podophyllotoxin probably acts through its direct fungicidal ability as well as through the follicular reaction it may produce.

Podophyllotoxin solutions should prove useful in the treatment of both new and recalcitrant M. audouini infections of the scalp.

Medical Arts Bldg. (2).

CONGENITAL ICHTHYOSIFORM ERYTHRODERMA

A Report of Two Cases in Siblings, One Complicated by Kaposi's Varicelliform Eruption

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AND
ARMISTEAD P. BOOKER, M.D.
CHARLOTTESVILLE, VA.

TWO CHILDREN in the same family with congenital ichthyosiform erythroderma have recently been available for detailed study. This condition is not seen often, and little information on the subject has been published in the current medical literature. In addition, one patient had what is thought to be the first recorded occurrence of Kaposi's varicelliform eruption as a complication of this disease, and his case is one of the few on record with complete autopsy findings.

Congenital ichthyosiform erythroderma was described by Brocq [1] in 1902, although it had been recognized as a clinical entity by Vidal [2] in 1882. However, according to Bruhns,[3] the first case was reported by Sangster in 1895. Important reviews of the literature were made by MacKee and Rosen [4] in 1917 and by Weiss and Tobias [5] in 1925. Laymon and Murphy [6] in 1948 presented a detailed report of the clinical features, histological aspects, and differential diagnosis of the disease. The cause of this unusual condition is not known. Consanguinity and a familial tendency to inheritance as a recessive trait have been noted.[7] Treatment is of little avail, and many agents have been used without lasting benefit.

Kaposi's varicelliform eruption or eczema herpeticum is usually a complication of a preexisting atopic dermatitis or eczema,[8] although a few cases have been

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1. Brocq, L.: Érythrodermie congénitale ichthyosiforme avec hyperepidermotrophie, Ann. dermat. et syph. **3**:1, 1902.

2. Vidal, cited by Laymon, C. W., and Murphy, R.: Congenital Ichthyosiform Erythroderma, Arch. Dermat. & Syph. **57**:615 (April) 1948.

3. Bruhns, C.: Ichthyosis, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1931, Vol. 8, Pt. 2, pp. 1-52.

4. MacKee, G. M., and Rosen, I.: Erythrodermie congénitale ichthyosiforme, J. Cutan. Dis. **35**:235 (April), 343 (May-June), and 511 (Aug.) 1917.

5. Weiss, R. S., and Tobias, N.: Congenital Ichthyosiform Erythroderma, Arch. Dermat. & Syph. **12**:182 (Aug.) 1925.

6. Laymon, C. W., and Murphy, R.: Congenital Ichthyosiform Erythroderma, Arch. Dermat. & Syph. **57**:615 (April) 1948.

7. Wile, U. J.: Familial Study of 3 Unusual Cases of Congenital Ichthyosiform Erythroderma, Arch. Dermat. & Syph. **10**:487 (Oct.) 1924.

8. Kaposi, M.: Pathology and Treatment of Diseases of the Skin, for Practitioners and Students, New York, William Wood & Company, 1895, p. 346. Lynch, F. W., and Steves, R. J.: Kaposi's Varicelliform Eruption, Arch. Dermat. & Syph. **55**:327 (March) 1947.

reported in other skin conditions.[9] There is considerable evidence that the eruption is a primary infection with the virus of herpes simplex.[10] The disease is self-limited except in the rare fatal cases. Treatment is usually symptomatic, and the value of antibiotic therapy is not known.

REPORT OF CASES

CASE 1.—R. W. F., a white male infant, was born at term in the University of Virginia Hospital on June 8, 1948, following a normal pregnancy and labor, except that the mother's membranes had ruptured spontaneously four days prior to delivery. He represented the second pregnancy of a normal, 17-yr.-old white woman. The mother's reaction to serologic test for syphilis was negative. Physical examination at birth showed a weight of 3,033 gm. (6 lb., 11 oz.), and other findings were normal except for intense redness of the cheeks, anterior aspects of the chest and knees, and the lateral surfaces of the arms. The redness was persistent, and, beginning on the third day of life, 10,000 units of aqueous penicillin were given intramuscularly every three hours for seven days. By the seventh day of life the skin condition had become dry and scaly and was more extensive, involving most of the face, parts of the anterior

Fig. 1 (Case 1).—Generalized erythematous eruption with extensive superficial exfoliation; patient 3 months old.

aspects of the trunk, legs, and feet, and the lateral surfaces of the arms and hands. There were several denuded areas on the right hand and on the nose. The skin of the palms and soles was not thickened. Results of laboratory examination at the age of one week were as follows: red blood count, 4,900,000 per cubic millimeter; hemoglobin, 18.0 gm. per 100 cc.; white blood count, 8,800 per cubic millimeter; a differential leukocyte count of 56% polymorphonuclear basophil leukocytes, 27% lymphocytes, 16% transitional monocytes, and 1% eosinophiles. There were a few large pathologic lymphocytes; some of the monocytes resembled atypical myelocytes, and there was slight toxic granulation and pyknotic degeneration. Urinalysis elicited no abnormalities except for a slight trace of albumin. Reactions to Wassermann, Kahn, and Kahn-titer tests were negative. Results of blood culture were negative. Roentgenograms of the long bones were normal. The patient was seen in dermatological consultation on the seventh day of life, and, in view of the physical findings and the history of the older sibling having been born with a similar

9. Fries, J. H.; Borne, S., and Barnes, H. L.: Varicelliform Eruption of Kaposi Due to Vaccinia Virus Complicating Atopic Eczema, J. Pediat. **32**:532 (May) 1948.

10. Ruchman, I., and Dodd, K.: Kaposi's Varicelliform Eruption: A Primary Infection with Herpes Simplex Virus, Pediatrics **1**:364 (March) 1948.

skin eruption, a diagnosis of congenital ichthyosiform erythroderma was made. His skin condition remained the same in spite of local applications. Except for an irregular gain in weight, his hospital course was otherwise uneventful. He was discharged on the 23rd day of life weighing 3,005 gm. (6 lb., 10 oz.).

He returned at the age of 6 weeks, and it was reported that his appetite was poor. There had been no gain in weight. The skin appeared thickened and had a generalized scaly, erythematous eruption, most marked over the upper portion of the chest and the flexor surfaces of the extremities. There was no overgrowth of the hair or nails. The scalp was crusted and scaly. When not restrained, the infant scratched the skin lesions vigorously, causing excoriation.

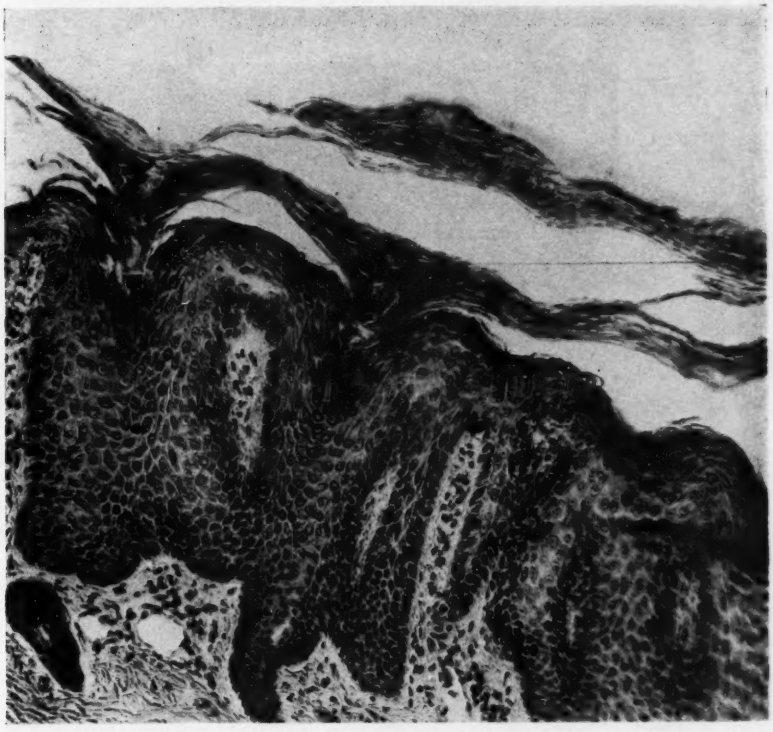

Fig. 2 (Case 1).—Photomicrograph (× 185) of section from flexor surface of left forearm, taken at autopsy, showing marked hyperkeratosis with plugging and parakeratosis, alternate areas of increase and decrease in granular layer, acanthosis, papillomatosis, and dilatation of superficial vessels. Biopsy at age of 3 months from left infrascapular area showed similar but less extensive changes.

The cervical, axillary, and inguinal lymph nodes were markedly enlarged. The liver edge was palpable 2 cm. below the right costal margin. Findings from a neurological examination were normal. A multivitamin preparation was prescribed.

Further review of the family history when the patient was 3 mo. old revealed that his parents were third cousins. A maternal aunt was reported to have had eczema which was not present at birth and which cleared by the time she was 2 years old. A skin condition similar to that of the patient was not known to have occurred in other members of the family except as

noted. His weight at that time was 3,859 gm. (8 lb., 9½ oz.), and his cutaneous status was unchanged (Fig. 1). His blood type was O Rh-positive. Biopsy of the skin was obtained (Fig. 2).

From 3 to 7 months of age his appetite and gain in weight remained poor, and he had two episodes of acute catarrhal otitis media. His skin remained red, dry, and scaly in spite of softening ointments, multivitamin preparations, and large doses of vitamin A.

Between 7 and 9 months of age, he was hospitalized three times because of vomiting, and on one admission also because of purulent otitis media. On all occasions his nutrition was poor, and his skin condition was unchanged, except for intermittent, superficial, almost-universal exfoliation with loss of large amounts of skin. Neurological examination elicited no abnormalities. His temperature was erratic, ranging from a minimum of 94.6 F. to a maximum of 102.0 F., most of the time being subnormal. Blood counts were normal except for a white count which

Fig. 3 (Case 1).—Typical lesions of Kaposi's varicelliform eruption; patient aged 13 months. Note umbilicated vesicles with crusting. Similar lesions were present on face.

ranged between 15,700 and 28,000 per cubic millimeter. Differential leukocyte counts on four occasions showed an eosinophilia ranging between 23% and 46%. Stools gave a negative reaction for parasites. Results of urinalyses were normal except for 1+ to 2+ reduction on four occasions. Fasting blood sugar was 76 mg. per 100 cc. Total serum protein was 4.8 gm. per 100 cc., with an albumin-globulin ratio of 1.3 to 1. The reaction to the tuberculin test with 0.1 cc. of 1:1,000 solution of old tuberculin was negative. Five milligrams of biotin administered subcutaneously every other day for three injections was not beneficial. A trial of milk substitute and omission of all solid food from the diet were without influence on the skin condition.

The infant was seen periodically thereafter as an outpatient because of poor appetite and loss of weight. At the age of one year he weighed 4,649 gm. (10 lb., 4 oz.) and was physically and mentally retarded.

He was readmitted to the hospital on July 30, 1949, aged 13 months, because of vesicular lesions on the face and neck of three days' duration, associated with fever. There had been no

known exposure to herpes or vaccinia. Physical examination showed a temperature of 104.4 F. and a weight of 4,252 gm. (9 lb., 6 oz). He was fretful, lethargic, and emaciated. There was a weeping, crusted, pustular eruption on the face, forehead, and the anterior surface of the neck, with erythematous, discrete, vesicular lesions bilaterally on the hands, arms, and knees. Laboratory examination on admission showed a red blood cell count of 4,400,000 per cubic millimeter, hemoglobin of 11.5 gm. per 100 cc., and white cell count of 11,200 per cubic millimeter,

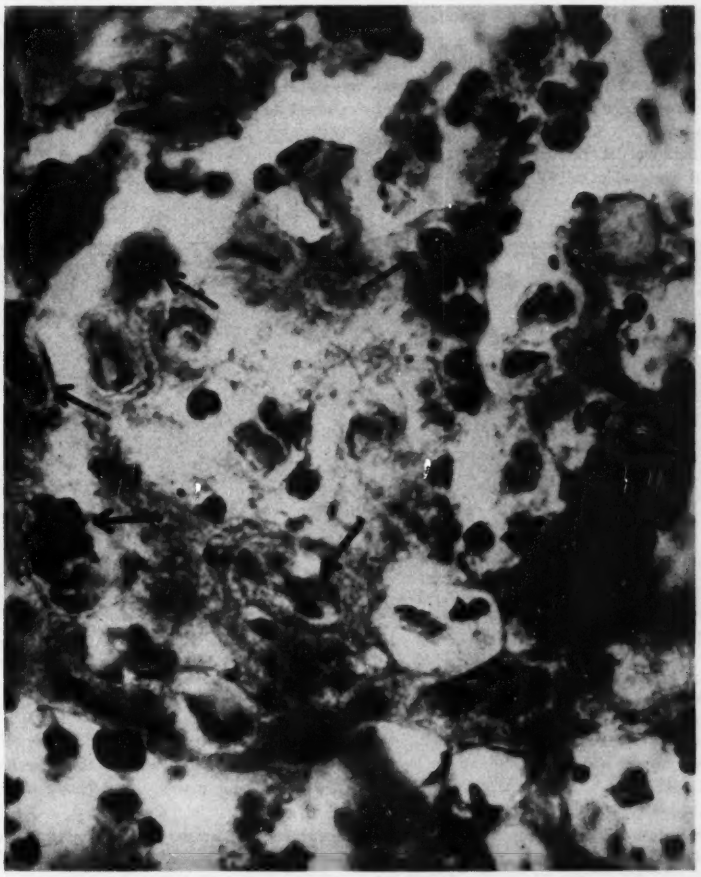

Fig. 4 (Case 1).—Photomicrograph of biopsy specimen of umbilicated vesicle showing inclusion bodies typical of herpes simplex infection; patient aged 13 months.

with a differential count of 56% polymorphonuclear basophil leukocytes, 16% lymphocytes, 5% monocytes, 21% eosinophiles, and 2% basophils. Upon examination, urine showed a slight trace of albumin and acetone, but was otherwise normal. Total serum protein was 5.0 gm. per 100 cc. with an albumin-globulin ratio of 1.5 to 1. Reactions of the blood to Wassermann and Kahn tests were negative.

A tentative diagnosis of pyoderma was suggested. Several days after admission it was noted that the vesicles on the face and extremities had become unbilicated, and a diagnosis of

Kaposi's varicelliform eruption was made. Biopsy of an umbilicated vesicle was obtained (Fig. 4). Aspiration of a vesicle for animal inoculation was attempted but was unsuccessful. Administration of 150,000 units of penicillin procaine intramuscularly once daily was begun on the second hospital day. The patient remained febrile, however, and was given aureomycin in addition, 25 mg. every four hours, orally, beginning on the sixth hospital day. By the 13th hospital day, the vesicles had disappeared and the temperature returned to normal. Use of aureomycin and penicillin was therefore discontinued. There was no apparent scarring.

The infant remained in the hospital from this admission until his death seven months later. He failed to maintain an adequate gain in weight in spite of blood transfusions, high caloric diet, gavage feedings, and vitamin supplements. Restraints and sedation were necessary. Local treatment with various antipruritic ointments was of no value. Testosterone propionate, 5 mg. twice weekly by intramuscular injection in two courses totaling five and one-half months, was of no benefit.

Additional laboratory studies showed the white blood cell count varying between 10,000 and 20,000 per cubic millimeter, with a persistent eosinophilia of 15 to 25%. Bone marrow examination on two occasions showed nothing suggestive of leukemia. Numerous urinalyses

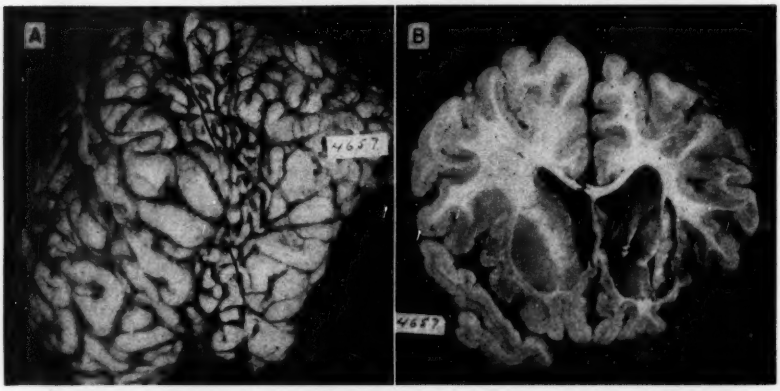

Fig. 5 (Case 1).—*A*, brain at autopsy showing extensive microgyria involving portions of the left frontal and temporal lobes. *B*, cross section of brain showing absence of anterior portion of left corpus striatum, including internal capsule and compensatory dilatation of left lateral ventricle.

elicited normal results, with no repetition of the reduction noted previously. Biopsy of an axillary lymph node showed mild chronic lymphadenitis. Roentgenograms of the long bones, heart, and lungs were normal. Cultures showed the blood, bone marrow, and lymph nodes to be negative for fungi.

In spite of all treatment the infant failed to improve and remained undeveloped and very emaciated. The skin continued to be erythematous, dry, and scaly, with marked fissuring and scaling of the scalp. Moderate alopecia and mild bilateral ectropion of the lower eyelids developed. The erythema decreased in severity with age, whereas the keratotic changes increased. At no time was there any overgrowth of the hair and nails. On March 2, 1950, the patient appeared cyanotic and was relieved with oxygen and caffeine. He remained listless and unresponsive in spite of supportive care and died on March 3, 1950, aged 21 months.

Autopsy Findings.—A complete autopsy showed generalized skin disease resembling ichthyosiform erythroderma, with consistent microscopic changes; underdevelopment of all portions of the body and generalized lymphadenopathy, particularly in the posterior cervical, occipital, and left inguinal regions; microgyria of the two left superior temporal convolutions of the brain, extending from the beginning of the sylvian fissure almost three-quarters the distance backward

and upward toward the superior longitudinal sulcus, with similar involvement of the portions of the left second and third frontal convolutions which lie just above Broca's area; absence of the anterior portion of the left corpus striatum, including the internal capsule except for a small inferior tip of the caudate nucleus; extensive compensatory dilatation of the left lateral ventricle with free communication into the third ventricle (Fig. 5); thickening, edema, and leukocytic infiltration of the meninges, particularly in the region of the microgyria; degeneration, softening, and vacuolization of the parenchyma just below the meninges in the area of the microgyria, without demonstrable vascular changes; bilateral bronchopneumonia; congestion of organs, and double pelvis and ureter of the right kidney.

CASE 2.—D. M. F., a white female infant, was born at term in the University of Virginia Hospital on Dec. 14, 1946, following an uncomplicated pregnancy and labor. This

Fig. 6 (Case 2).—Normally developed, 3¼-year-old child, showing abundant hair, dry, scaly, erythematous, keratotic lesions, especially on the face and extremities, and keratoderma of the palms.

child is the older sibling of the infant described in Case 1. Physical examination at birth showed a weight of 3,515 gm. (7 lb., 12 oz.), and findings were normal except for an erythematous eruption on the extremities and on the back, which became dry and scaly in about three days. Laboratory examination showed a red blood cell count of 5,600,000 per cubic millimeter, hemoglobin 18.5 gm. per 100 cc., and white blood cell count 11,000 per cubic millimeter; differential leukocyte count showed 50% polymorphonuclear basophil leukocytes, 39% lymphocytes, and 10% transitional monocytes. There were a few large pathologic lymphocytes, some of the myelocytes were atypical, and there was slight toxic granulation. Wassermann reaction and culture of the blood were negative. The skin condition was diagnosed as congenital ichthyosis.

In spite of local applications, it rapidly became generalized. The infant's hospital course was uneventful except for an irregular gain in weight, and she was discharged on the 22d day of life weighing 3,325 gm. (7 lb., 5¼ oz.).

She returned at the age of one month because of acute purulent otitis media which required myringotomy and was satisfactorily treated with sulfadiazine. Her skin was red and dry.

At the age of 3 months she weighed 5,216 mg. (11 lb., 8 oz.), and her general development was normal. Her skin showed an erythematous, fine scaly eruption which was generalized except for several areas on the trunk. The condition was most severe on the face and on the extensor surfaces of the extremities. The palms showed marked keratoderma, but the soles were not involved.

General physical development was normal at one year. The skin eruption was unchanged, except that there was moderate excoriation as a result of scratching, and there was severe exfoliation and crusting of the scalp.

In June, 1948, the younger sibling was born, and at that time the correct diagnosis of congenital ichthyosiform erythroderma was made for this child.

At the age of 21 months she weighed 10.9 kg. (24 lb., 3½ oz.). The skin condition was unimproved, and there was marked enlargement of the cervical, axillary, and inguinal lymph nodes. Biopsy of the skin was obtained. Blood group determination showed the blood type was O Rh-positive.

When last examined at 3½ years she weighed 13.6 kg. (30 lb.), and her general physical and mental development were satisfactory (Fig. 6). Her skin had failed to improve in spite of softening ointments and large doses of vitamin A. With the passage of time the eruption had become more dry and scaly and less red. The skin condition had tended to improve in the summer and to become more severe in the winter. At no time did it disappear.

COMMENT

The findings, including the biopsies of the skin, were characteristic of congenital ichthyosiform erythroderma in both patients. The clinical course and autopsy studies in the younger child tend to verify the observation of previous writers that some patients with this disease show malnutrition and faulty development.[7] A familial occurrence was present, as noted in the past, but sex-linkage was not apparent.

The diagnosis of Kaposi's varicelliform eruption was supported by biopsy of an umbilicated vesicle which showed the cutaneous changes characteristic of a virus infection and in which many inclusion bodies typical of herpes-simplex infection were demonstrated. Such inclusion bodies are found also in herpes zoster and in varicella, but the latter two diseases seem to have been ruled out in this case. Clinically, the lesions did not resemble those of herpes zoster, particularly since they were bilateral. Also, varicella later developed during a mild epidemic in the hospital ward. Blood serum secured on the 10th day of the eruption contained no neutralizing antibodies for herpes simplex, whereas specimens taken during the fifth week after onset showed antibodies present in a titer greater than 1 : 16. It is believed that this may be interpreted as diagnostic of a primary infection with herpes simplex virus. An attempt to isolate the virus late in the course of the disease was not successful.

SUMMARY

The cases of two children from the same family with congenital ichthyosiform erythroderma are presented.

The younger sibling's illness was complicated by Kaposi's varicelliform eruption, and this is the first known report of that disease in congenital ichthyosiform eryth-

roderma. The findings tend to substantiate the belief that Kaposi's varicelliform eruption is a primary infection with the virus of herpes simplex.

Complete autopsy was obtained on the younger child and showed the additional findings of extensive microgyria involving portions of the left frontal and temporal lobes and absence of the anterior portion of the left corpus striatum, including the internal capsule.

It will be of interest to note the outcome in future pregnancies of the mother of these children.

ADDENDUM

Since the preparation of this report, the mother of these children has been delivered of a third, full-term, girl infant whose skin appeared normal at birth and at the time of discharge from the hospital on the fifth day of life.

2 Chambers St.
University of Virginia Hospital.

Dr. Harvey Blank of the University of Pennsylvania School of Medicine assisted in the demonstration of the inclusion bodies, in performance of the neutralizing antibody tests, and in interpretation of the data.

LICHEN SCLEROSUS ET ATROPHICUS AND RELATED DISORDERS

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MINNEAPOLIS

FOR MANY years confusion has existed concerning the relationship of lichen sclerosus et atrophicus to balanitis xerotica obliterans, kraurosis penis and vulvae, atrophic lichen planus, and guttate morphea. The purpose of this paper is to review the clinical and histologic features of these diseases and to discuss their relationship.

LICHEN SCLEROSUS ET ATROPHICUS

The paper by Montgomery and Hill [1] was a great help in clearing the confusion which existed in the terminology applied to lichen sclerosus et atrophicus. In reviewing the literature they found that names which had been applied to this disease included lichen planus sclerosus et atrophicus, lichen planus morphoeicus, white spot disease, Unna's card-like scleroderma, lichen albus of von Zumbusch, and chronic atrophic lichenoid dermatitis of Csillag. Apparently most dermatologists now feel that these terms should be abandoned, especially white spot disease which has been used loosely to include both lichen sclerosus and guttate morphea.

The characteristic lesion of lichen sclerosus et atrophicus is an irregular, often polygonal, flat-topped papule. The white or yellowish-white color of the lesions is striking. They may be discrete or may coalesce to form plaques, but in most cases both types of lesions are present. The presence of dells and of follicular plugging is regarded as an important diagnostic aid. The papules, as a rule, are firm to the touch, neither elevated nor depressed, although slight elevation may be present. As a rule, no areola is seen, but at times a moderately pigmented zone may surround the papules. When plaques are formed, the outline of the individual papules forming the patches can usually be determined. As time goes on and the lesions become atrophic, the keratotic plugs and central delling may become more prominent. Early in the course of the disease, however, keratotic plugs or depressions may not be recognized clinically. If and when the lesions undergo involution, they may do so without leaving a trace or leaving a white parchment-like or tissue-like wrinkling. In Montgomery and Hill's series of 46 cases the disease was about six times as frequent among women as among men. The disease occurred most frequently in middle-aged persons, although no relationship to the menopause was established. Montgomery and Hill stated that the average age of men at the onset

From the Division of Dermatology, University of Minnesota (Henry E. Michelson, M.D., Director) and the Department of Dermatology, Minneapolis General Hospital (Carl W. Laymon, M.D., Director).

1. Montgomery, E., and Hill, W. R.: Lichen Sclerosus et Atrophicus, Arch. Dermat. & Syph. **42**:755 (Nov.) 1940.

was 43 and that of the women, 50. Laymon,[2] however, observed three cases in girls below the age of 6 years in whom the lesions were limited to the anogenital region. The areas most commonly involved are the upper portions of the trunk, especially in the clavicular and scapular regions, the neck, axillae, and forearms, but apparently the disease may be observed anywhere on the body below the line of the neck. Montgomery and Hill observed the disease in 38 women, 20 of whom presented involvement of the vulva and anus as well as other parts of the body. In six of the patients the disease was limited to the anogenital region. In general, the lesions tend to be symmetric. Involvement of the oral mucous membranes apparently does not occur. In most instances the disease is relatively asymptomatic, although when it occurs on the vulva moderate to severe pruritus may be present. The individual lesions tend to persist indefinitely, and there is no specific or satisfactory treatment, although involution has been observed following various types of therapy.

The chief histologic features of lichen sclerosus et atrophicus is the band of homogenization in the upper part of the cutis. In all probability this begins as an edema beneath the epidermis with resultant flattening of the rete pegs, ridges, and papillary bodies. Lacunas beneath the epidermis may be observed, which probably result from lymphedema. A perivascular infiltrate of varying degree is seen in the mid-cutis beneath the area of homogenization, which at times appears as a band. There is usually pressure-atrophy of the epidermis, with hyperkeratosis and keratotic plugging. There is no appreciable destruction of elastic tissues, although they may appear spread as a result of the edema. Montgomery believes that there are no obliterative changes in the deeper blood vessels in lichen sclerosus et atrophicus.

BALANITIS XEROTICA OBLITERANS

Balanitis xerotica obliterans (post-operationem) is the term which Stühmer [3] used in 1928 to describe an atrophic, shrinking process involving the glans penis and prepuce and frequently leading to urethral stenosis. On the basis of his first five cases Stühmer concluded that, although there was a close relationship among various sclerosing processes of the male genitals described in the literature under the titles of leukoplakia and kraurosis, the disorder which he described was singular in that it developed in men in the second and third decades and followed circumcision for phimosis. Stühmer's euphonious title became a popular one, and several cases of sclerotic atrophic dermatoses of the glans and prepuce have been reported before various societies under that name, and several contributions devoted to the subject have appeared. My observations are based on the study of approximately 30 cases of balanitis xerotica obliterans observed at the University of Minnesota and Minneapolis General Hospitals and in private practice, some of which were previously discussed by Freeman and Laymon.[4]

2. Laymon, C. W.: Lichen Sclerosus et Atrophicus in Childhood, Arch. Dermat. & Syph. **52**:351 (Nov.-Dec.) 1945.

3. Stühmer, A.: Balanitis Xerotica Obliterans (post-operationem), und ihre Beziehungen zur "Kraurosis Glandis et Praeputii Penis," Arch. Dermat. u. Syph. **156**:613, 1928.

4. (*a*) Freeman, C., and Laymon, C. W.: Balanitis Xerotica Obliterans, Arch. Dermat. & Syph. **44**:547 (Oct.) 1941. (*b*) Laymon, C. W., and Freeman, C.: Relationship of Balanitis Xerotica Obliterans to Lichen Sclerosus et Atrophicus, ibid. **49**:57-59 (Jan.) 1944.

The disease occurred at various ages ranging from 22 to 65. A relation to circumcision could not be determined in any of the patients, and a history of repeated attacks of balanoposthitis was noticeably absent except in one. The early symptoms of the disease vary in acuity and intensity. They may be of insufficient severity to force the patients to seek medical advice, and consequently when the patient is first seen by a physician the disease is in full development. The early changes are especially apt to remain unnoticed if the prepuce is long. They may consist of only a few erythematous areas on the prepuce or glans. The disorder, however, may appear abruptly and undergo an extremely stormy course in its early phases. There may be intense pain, itching, burning, and prickling, with profuse urethral secretion. In one instance sloughing of the distal half-centimeter of the urethra occurred, with the result that it hung from the meatus and had to be clipped. Later in the course of the disease there may be pain on erection, diminution in sensation of the glans and disturbance of the sexual function. As a rule, balanitis xerotica obliterans is chronic and slowly progressive. There may be, however, a somewhat cyclic course characterized by periods of improvement in which the skin apparently becomes less sclerotic and the urethral stenosis less intense. In patients who have not been circumcised, there is an almost constant involvement of the prepuce in the form of a constricting, sclerotic band which is located 1 or 2 cm. from the distal end. As the disease progresses, the coronal sulcus may partially or completely disappear, and the frenulum may be obliterated or sclerosed. There may be adhesions between the prepuce and the glans.

The involvement of the glans may or not be diffuse. If it is, the glans is white, bluish-white, or yellowish-white. If it is not diffuse, the admixture of the white plaques and the normal red tissue of the glans may give rise to the mottled appearance. Areas of telangiectasia may be present which simulate radiodermatitis. The glans may appear shriveled, although when stretched between the fingers the skin is smooth and shiny. The lesions may resemble parchment. The affected tissues are more friable than normal, with the result that tiny fissures appear, especially on the prepuce and the frenulum. Erosions and hemorrhagic or serous subepidermal bullae, especially near the meatus, may accompany the cicatricial changes. Carcinoma may be an eventual development, as exemplified in cases described by Stühmer, Frühwald [5] and Grütz.[6]

Another noteworthy and constant feature of balanitis xerotica obliterans is the gradual narrowing of the urethral meatus, often leading to complete stenosis, which renders urination increasingly difficult and finally impossible. The potential dangers of the meatal stricture should be remembered since it may lead to urinary retention, damage to the posterior urethra, bladder, and kidneys, or even to perineal phlegmon.

Histologically, inflammatory changes predominate in the earlier changes of the disease. The epithelium is invaded by polymorphonuclear leucocytes, and at first there is an abundant diffuse cellular infiltrate in the papillary portion of the edematous cutis, with large numbers of the same type of cells. Later, the relative number of lymphocytes increases, and epithelioid and plasma cells may be present.

5. Frühwald: Peniscarcinom nach Balanitis xerotica obliterans (Stühmer), Zentralbl. Haut- u. Geschlechtskr. **50**:98, 1935.

6. Grütz, O.: Beiträge zur Klinik der Balanitis xerotica obliterans, Dermat. Wchnschr. **105**:1206, 1937.

In the subacute phases the lymphocytic infiltrate becomes arranged about the vessels. In the fully developed condition there is distinct atrophy of the epidermis but with relative and absolute hyperkeratosis. There may be a moderate degree of intracellular edema in the upper portions of the epidermis and slight liquefaction degeneration of the basal cell layer. A sprinkling of lymphocytes may be noted directly beneath the basal layer. Perhaps the most striking histologic feature of balanitis xerotica obliterans is the band of homogenization in the upper portion of the cutis. This area appeared relatively acellular and edematous and may show diminution or complete disappearance of the elastic tissue. To this point the histologic pictures of balanitis xerotica obliterans and lichen sclerosus et atrophicus are practically identical. In balanitis xerotica obliterans, however, the band-like formation of the infiltrate is not as frequently seen as in lichen sclerosus et atrophicus. In the middle and deeper portions of the cutis a lymphocytic perivascular infiltrate is present, as a rule.

KRAUROSIS PENIS

In 1908 Delbanco[7] published a report of three cases of a condition which he termed kraurosis glandis et praeputii penis, characterized by a progressive, atrophic retraction of the glans and inner fold of the prepuce, leading to stenosis of the urethral meatus. The disease was accompanied by intense itching and disagreeable paresthesias. Delbanco stated his belief that kraurosis was a disease sui generis differing from leukoplakia as described by Kraus and Fuchs. When one analyzes carefully and compares the clinical and histologic features which have been described as representative of balanitis xerotica obliterans and kraurosis penis, one is forced to admit that there are no essential differences. Both are chronic, atrophic, sclerosing processes of the prepuce and glans, leading to urethral stenosis. Both show atrophy of the epidermis, edema and homogenization of the cutis, inflammatory changes about the blood vessels, and diminution or loss of elastic tissue. Stühmer admitted that the fundamental changes in the two diseases were the same, but stated the belief that balanitis xerotica obliterans should be set aside as a separate disease entity because (1) it occurred in younger patients, (2) it followed some operative procedure, and (3) the annoying and itching paresthesias which presumably characterize kraurosis penis were not prominent features in this disease.

KRAUROSIS VULVAE

Kraurosis vulvae was defined concisely by Darier[8] as follows: The term kraurosis (Breisky), the meaning of which is sufficiently vague, has been defined and should be reserved for a sclerosing progressive atrophy of the mucocutaneous teguments of the vulva, leading gradually to stenosis of the vaginal orifice, disappearance of the labia minora, frenulum, and clitoris, and flattening of the labia majora. The mucosa of the parts involved is always smooth, shining, and dry. The color is white, waxy-yellow, red, or spotted. The complication by leukoplakia is frequent, and in such cases cancer is to be feared. It has been stated that kraurosis should be distinguished from simple senile atrophy of the vulva occurring post-

7. Delbanco: Kraurosis Glandis et Praeputii Penis, Arch. Dermat. u. Syph. **91**:384, 1908.

8. Darier, J.: Précis de dermatologie, ed. 4, Paris, Masson & Cie, 1928, pp. 276, 465, and 994.

menopausally. In kraurosis vulvae the atrophic skin is said to merge gradually with the normal skin, and kraurosis does not as a rule extend beyond the inner aspect of the labia majora.

Montgomery and Hill believed that perianal involvement, which occurs in lichen sclerosus et atrophicus, does not occur in kraurosis. These workers also felt that atresia and stenosis of the vaginal orifice, which is characteristic of kraurosis vulvae, does not occur in lichen sclerosus. They admitted that the histologic changes which occur in lichen sclerosus and kraurosis are almost identical. In kraurosis there are relative and absolute hyperkeratosis, atrophy of the rest of the epidermis, some liquefaction necrosis of the basal layer, and the same type of peculiar homogenization and separation of elastic tissue fibers in the upper part of the cutis as is seen in lichen sclerosis resulting from lymphedema and dilatation of lymphatic spaces, vessels, and capillaries. The only differences which they noted were the presence of definite atrophy of the cutis as a whole and mild arteriosclerotic changes in the deeper vessels in true kraurosis. They stated that keratotic plugging as seen in lichen sclerosus is usually not present in kraurosis.

LICHEN PLANUS

It is my opinion that lichen planus is not related to lichen sclerosus et atrophicus, balanitis xerotica obliterans, and kraurosis vulvae. Lesions of lichen planus limited to the penis may present a superficial similarity to balanitis xerotica obliterans. Freeman and Laymon never observed the two disorders in the same patient, nor to my knowledge has such an association been reported in the literature. If characteristic lesions of lichen planus can be found elsewhere on the skin or mucous membranes, the diagnosis of the penile lesions or vulvar lesions presents no difficulty. Lesions of lichen planus on the genitals are more apt to be elevated in contrast to the atrophic plaques of lichen sclerosus, and urethral stenosis is not present in the former. In typical cases of the two diseases, histologic studies also form a reliable means of differentiation. Except in the rare atrophic forms of lichen planus there is an increase in the stratum corneum and stratum granulosum with varying degrees of acanthosis, in contrast to distinct atrophy in lichen sclerosus. The sharply limited band of infiltrate in the upper part of the cutis in lichen planus persists even in the atrophic form of the disease in which the epidermis is thin. In cases of lichen sclerosus, the area which is the site of the infiltrate in lichen planus appears edematous and homogenized. The latter feature is not observed in lichen planus.

CIRCUMSCRIBED SCLERODERMA

The relationship of circumscribed scleroderma to lichen sclerosus is not exactly determined. Montgomery and Hill concluded that lichen sclerosus et atrophicus presented typical clinical and histologic changes which were distinct from guttate morphea and encountered no transitional form between lichen sclerosus et atrophicus and guttate morphea in a series of 46 cases of lichen sclerosus et atrophicus. They believed that most of the cases reported in the literature probably represented instances of one disease or another. I have, however, observed three cases in which lesions of morphea and lichen sclerosus et atrophicus coexisted in the same patient. This may have been strictly coincidental, although it is difficult to say that circumscribed scleroderma and lichen sclerosus et atrophicus are not at least closely related to one another. Scleroderma occurs extremely rarely on the male genitals.

Pautrier and Camus,[9] in 1932, reported the case of a patient who presented a ring of scleroderma about the glans and prepuce. In 1934 Gougerot, Degos, and Roulle [10] described two similar cases and stressed the difficulty in making such a diagnosis if there were no lesions elsewhere on the body. In 1939 Gougerot and Basset [11] reported the case of a boy, aged 19, in whom two sclerotic rings developed on the prepuce three weeks after an attack of balanitis. In this case the urethral meatus contracted and infiltrated. In the discussion of the case, Clemont Simon proposed a diagnosis of balanitis xerotica obliterans. Touraine also related an interesting case which he had studied in which there was typical balanitis xerotica obliterans with scleroderma *en bande* of the abdomen and inguinal regions. For this reason he felt that balanitis xerotica obliterans was a part of scleroderma. The histologic pictures in the two disorders, however, are not at all alike. In the former there is an actual increase in number and thickening of the individual connective tissue fibers throughout the whole cutis, as contrasted with an edematous, homogenized zone in the upper part of the cutis in balanitis xerotica obliterans.

COMMENTS

The association of lichen sclerosus et atrophicus and balanitis xerotica obliterans was not noticed in any of the 18 patients whose cases Freeman and Laymon discussed in 1941, although, unfortunately, no careful search for lesions elsewhere on the body was made. Attention was called to a possible relationship between the two diseases in 1940 at a meeting of the Minnesota Dermatologic Society, where Dr. Fred Becker presented a patient with unmistakable papules of lichen sclerosus et atrophicus in the clavicular and scapular regions and on the shaft of the penis and scrotum, along with characteristic sclerosing lesions of balanitis xerotica obliterans on the prepuce and glans. It was impossible to obtain a specimen for biopsy from the glans, although the histologic picture of the lesion from the clavicular region was that of lichen sclerosus et atrophicus.

Fabry,[12] in 1928, reported a case in which there was, in all probability, a similar association. The patient, aged 35, was said to have had "kraurosis penis" and "white spot disease" on the scrotum. Judged from the photomicrograph in the article, the eruption on the scrotum was lichen sclerosus et atrophicus. In 1944 Laymon and Freeman [4b] reported the cases of four additional patients who had plaques of lichen sclerosus et atrophicus on the body in association with characteristic lesions of balanitis xerotica obiterans on the glans and prepuce and isolated papules of lichen sclerosus et atrophicus on the shaft of the penis. Fully developed balanitis xerotica obliterans presents a characteristic picture. It is obvious to dermatopathologists that the histologic features of balanitis xerotica obliterans and lichen sclerosus et atrophicus are identical. In one of the cases reported by Laymon and Freeman, specimens from the clinical lesions of lichen sclerosus et atrophicus

9. Pautrier, L. M., and Camus, R.: Sclérodermie annulare du gland, Bull. Soc. franç. dermat. et syph. **39**:304, 1932.

10. O'Gougerot, H.; Degos, and Roulle, S.: Sclérodermie de l'anneau preputial, Bull. Soc. franç. dermat. et syph. **41**:896, 1934.

11. Gougerot, H., and Basset, A.: Sclérodermie en deux anneaux concentriques du gland et du sillon balano-préputial, Bull. Soc. franç. dermat. et syph. **46**:1326, 1939.

12. Fabry, J.: Über einen Fall von Kraurosis penis bei gleichzeitigem Bestehen von Weissflecken am Skrotum, Dermat. Wchnschr. **86**:7, 1928.

on the body, as well as plaques on the genitals regarded as balanitis xerotica obliterans, showed no noteworthy differences. Lichen sclerosus et atrophicus can occur on the male genitals in two forms: (1) as isolated papules on the shaft and (2) as a constricting band about the prepuce, with plaques on the glans and urethral stenosis. Both forms may coexist, and both may occur alone or with ordinary lesions of lichen sclerosus et atrophicus elsewhere on the body.

The opinion has been previously expressed that the terms balanitis xerotica obliterans and kraurosis penis have been applied to identical disorders and that there are no clinical or histologic differences.

If the term leukoplakia is reserved for patchy, circumscribed, thickened, smooth or rough, milky, opalescent plaques which rarely occur in the glans or prepuce, there is little confusion with balanitis xerotica obliterans. Leukoplakia of the genitals is identical with that occurring in the mouth. It is a hypertrophic, hyperplastic process rather than an atrophic, retractive one. It may occur alone, or in conjunction with atrophic lesions as in cases reported in the literature by Kraus, Genar, and Nielsen. The same frequent association of kraurosis and leukoplakic vulvitis has been emphasized by Montgomery, Counseller, and Craig.[13] There is considerable difference of opinion concerning the relationship of lichen sclerosus et atrophicus to kraurosis vulvae. A postmenopausal woman was examined recently at the Minneapolis General Hospital who presented sclerosing atrophy of the vaginal orifice, with disappearance of the labia minora and clitoris and flattening of the labia majora. The mucosa of the involved areas was smooth, shining, dry, and white. No involvement of the adjoining skin was observed, and the perianal area was free. The histologic features were indistinguishable from those regarded as characteristic of lichen sclerosus et atrophicus. No obliterative changes in the vessels were observed. It is my opinion, based on personal observations and discussions with many dermatologists of wide experience, that kraurosis vulvae is an extremely rare disorder. It seems practically impossible to differentiate two disorders, such as lichen sclerosus et atrophicus limited to the anogenital region and kraurosis vulvae, in which both clinical and histologic features are practically identical. Leukoplakic complications have been observed in lichen sclerosus limited to the male genitals (balanitis xerotica obliterans or kraurosis penis), just as they have been in kraurosis vulvae. Epitheliomatous degeneration has been reported in balanitis xerotica obliterans (kraurosis penis), just as it has been in kraurosis vulvae. Delling and keratotic plugging, which have been said to be absent in kraurosis vulvae, are not an infallible diagnostic aid, since they are inconstant in lichen sclerosus et atrophicus. It would seem that there is more evidence in favor of classifying kraurosis vulvae as a type of lichen sclerosus et atrophicus affecting the female genitals than there is in classifying it as a distinct entity, for the aforesaid reasons.

SUMMARY AND CONCLUSIONS

1. Lichen sclerosus et atrophicus is not related to the atrophic form of lichen planus.

2. Balanitis xerotica obliterans and kraurosis penis are terms which have been applied to the same disease.

13. Montgomery, H.; Counseller, V. S., and Craig, W. M.: Kraurosis, Leukoplakia and Pruritus Vulvae, Arch. Dermat. & Syph. **30**:80 (July) 1934.

3. Balanitis xerotica obliterans (kraurosis penis) represents a form of lichen sclerosus et atrophicus involving the genitals.

4. Lichen sclerosus et atrophicus may occur on the male genitals as (1) isolated papules on the shaft or (2) sclerotic preputial and urethral involvement with patches on the glans.

5. Both types of genital involvement may occur alone or with lesions on the body, and all forms present the same histologic features.

6. There is more evidence favoring the classification of kraurosis vulvae with lichen sclerosus et atrophicus than for regarding it as a distinct entity, since the clinical and histologic features seem practically indistinguishable.

7. Because of distinct clinical and histologic differences, it is impossible to say that forms of circumscribed scleroderma and lichen sclerosus are the same. However, because characteristic clinical and histologic lesions of both disorders have occurred in the same patient, they probably are closely related to each other.

TREATMENT OF URTICARIA AND DERMATITIS VENENATA WITH CORTICOTROPIN (ACTH) AND CORTISONE

CAPTAIN GORDON H. EKBLAD (MC), U.S.N.

BENEFICIAL effects from employing corticotropin (ACTH) have been reported in two patients with penicillin urticaria and in one with a severe exfoliative dermatitis due to iodine by Bordley, Harvey, and Howard.[1] Randolph and Rollins [2] reported temporary beneficial results in two cases of atopic dermatitis treated with corticotropin. Conn [3] reported beneficial results in a case of giant urticaria due to food sensitivity. Gordon [4] reported a dramatic clinical response in a case of urticaria and angioneurotic edema treated with corticotropin. Medical summaries on the use of corticotropin and cortisone, as well as commercial pamphlets on these products, frequently refer to the beneficial effects of corticotropin or cortisone in allergic dermatoses, although they rarely mention specific cases.

This report concerns 27 cases of urticaria and other allergic dermatoses treated with corticotropin and cortisone. The 27 cases reported are those of white male service and veteran patients hospitalized at the United States Naval Hospital, Oakland, Calif., during January and February, 1951. In 11 of the 15 cases of acute urticaria the condition was caused by allergy to penicillin, and in the other four cases the acute urticaria was due to a sulfonamide drug, a food allergy, paint fumes, and an undetermined cause, respectively. There were five cases of chronic urticaria, one of which was due to tetanus toxoid, one due to amebiasis and hepatitis, and three of undetermined origin. There were seven patients with miscellaneous allergic dermatoses, five of which were diagnosed as dermatitis venenata, one as atopic dermatitis, and one as fungus "id" reaction.

The method of using cortisone and corticotropin was, in general, to treat for one day and to observe the short-term effects. When one agent was unsuccessful, the other was tried. Antihistaminics given in conjunction with intravenous calcium gluconate were also compared with cortisone and corticotropin as therapeutic agents.

Data on the 15 acute urticarial cases are summarized in Table 1.

This article has been released for publication by the Division of Publications of the Bureau of Medicine and Surgery of the United States Navy. The opinions expressed are those of the author, and do not necessarily reflect the views of the Navy Department.

1. Bordley, J. E.; Harvey, A. M.; Howard, J. E., and Newman, E. V.: Preliminary Report on the Use of ACTH in the Hypersensitive State, in Proceedings of the First Clinical ACTH Conference, edited by J. R. Mote, Philadelphia, The Blakiston Company, 1950, p. 470. Bordley, J. E., and others: Preliminary Observations on the Effect of ACTH in Allergic Diseases, Bull. Johns Hopkins Hosp. **85**:396 (Nov.) 1949.

2. Randolph, T. G., and Rollins, J. P.: Relief of Allergic Diseases by ACTH Therapy, in Proceedings of the First Clinical ACTH Conference, edited by J. R. Mote, Philadelphia, The Blakiston Company, 1950, p. 483.

3. Conn, J. W., in discussion on Randolph and Rollins.[2]

4. Gordon, E., in discussion on Randolph and Rollins.[2]

TABLE 1.—*Summary of Data on Acute Urticaria*

Case No.	Name, Age	Diagnosis	Response to			Comment
			Corticotropin	Cortisone	Antihistaminics with Calcium Gluconate*	
1	BVD, 20	Angioneurotic edema, severe; penicillin allergy	A	C (?)	..	H-1, cortisone 100 mg. × 1 H-3, ACTH 10 mg. × 1 (total dose)
2	EJM, 25	Urticaria; penicillin allergy	A	..	..	H-1, received diphenhydramine I. V. with temporary relief H-3, ACTH 10 mg. × 3 (30 mg.)
3	KP, 30	Urticaria, fairly severe; penicillin allergy	A	..	..	H-1, ACTH 20 mg. × 3 (60 mg.)
4	JWN, 29	Urticaria, severe; penicillin allergy	A	..	..	H-2, ACTH 10 mg. × 4 (40 mg.); dramatic response
5	TLD, 25	Urticaria; penicillin allergy	A	..	..	H-1, ACTH 10 mg. × 4 (40 mg.); poor response H-2, ACTH 20 mg. × 4 (80 mg.); good response
6	DWA, 19	Angioneurotic edema, severe; penicillin allergy	..	C	..	H-1, cortisone 25 mg. × 4 (100 mg.); minimal pruritus for 2 days
7	GBD, 19	Urticaria, severe; penicillin allergy	A	c	ah	H-1, cortisone 200 mg. (1 dose) H-2, ACTH 10 mg. × 4 (40 mg.); recurrence 7 days after ACTH H-14, cortisone 50 mg. × 2 (100 mg.) H-15 and H-16, antihistaminics with calcium gluconate
8	DWM, 40	Urticaria; penicillin allergy	a	c (?)	..	H-1, cortisone 50 mg. × 1 H-2, ACTH 20 mg. × 1 H-3, cortisone 25 mg. × 4 (100 mg.)
9	JEB, 37	Urticaria, severe; penicillin allergy	a	..	AH	H-1, ACTH 20 mg. × 2 (40 mg.) H-2, antihistaminics with calcium gluconate; prompt relief for 3 hr. H-3, antihistaminics with calcium gluconate and 20 mg. ACTH; good response with only minimal pruritus controlled by tripelennamine for 3 days, then well
10	CWF, 27	Urticaria; penicillin allergy	..	C	..	H-1, cortisone 25 mg. × 2 (50 mg.)
11	CJB, 30	Urticaria; penicillin allergy	A	C	ah	H-2 and H-3, antihistaminics with calcium gluconate H-4, ACTH 20 mg. × 2 (40 mg.) H-8, recurrence, and received cortisone 50 mg. × 2 (100 mg.); recurrent transient pruritus for 2 wk. not requiring treatment
12	JNS, 20	Giant urticaria; cause undetermined	..	c	AH	H-1, cortisone 25 and 50 mg. (75 mg.) H-2, H-5, H-6, antihistaminics with calcium gluconate; no recurrence after H-6
13	DFF, 25	Urticaria and papular rash; sulfonamide allergy	A	..	..	H-1, ACTH 20 mg. × 3 (60 mg.)
14	EM, 40	Papular urticaria, severe pruritus; food allergy	A	C	AH	H-1, H-2, H-5, ACTH 10 mg. × 4 (40 mg. daily); dramatic relief but recurrence in 6-12 hr. H-4, cortisone 25 mg. × 4 (100 mg.); fair relief H-6, cortisone 50 mg. × 4 (200 mg.); dramatic relief, recurrence H-7 through H-13 and H-16 through H-19, antihistaminics with calcium gluconate; good relief for 4-5 hr. (lesions gradually subsiding) antihistaminics with calcium gluconate H-14, poor relief on antihistaminics alone H-15, poor relief on calcium gluconate I. V., alone
15	BWG, 32	Urticaria, severe; allergy to paint fumes	A	..	..	H-2, ACTH 10 mg. (total dose); mild recurrent fleeting lesions for 2 wk. (received antihistaminics p. r. n. first 4 days)

* Antihistamine dosage was 100 mg. orally every 6 hr. concurrent with 1 gm. calcium gluconate intravenously twice daily.

Key to symbols: A, good response to ACTH; a, poor response to ACTH; C, good response to cortisone; c, poor response to cortisone; AH, good response to antihistaminics with calcium gluconate; ah, poor response to antihistaminics with calcium gluconate; H-1, first hospital day, etc.

ACUTE URTICARIA

As Table 1 shows, 12 of the patients with acute urticaria were treated with corticotropin. Ten of these 12 patients had good response to corticotropin. Two of the patients failed to respond to the dosages used (20 mg. in one case, and 40 mg. in the other). Three of the patients showing good initial response to corticotropin later relapsed and were re-treated either with corticotropin, cortisone, or antihistaminics combined with intravenous calcium gluconate. Three other patients, although showing prompt response to corticotropin, continued to show a minimal pruritus for 2 to 14 days, and two of these were treated symptomatically with antihistaminics for two and four days, respectively.

Eight of the patients with acute urticaria were treated with cortisone. Five of the cortisone-treated patients showed good response, while three showed poor response. Those showing good response to cortisone did not, in general, show as marked improvement as those treated with corticotropin.

Two patients received no benefit from antihistaminics with intravenous calcium, but responded promptly to corticotropin. Three patients had good relief following antihistaminics with intravenous calcium, but relief was temporary, all symptoms recurring in two to four hours. The case of one of the latter was interesting in that he showed poor response to corticotropin, prompt but temporary relief with antihistaminics and intravenously injected calcium, and then showed progressive relief with corticotropin combined with antihistaminics and intravenously administered calcium, with no recurrence of the lesions.

REPORT OF CASES

Case 4.—JWN, age 29, presented generalized, extremely severe, giant urticaria involving practically the entire body, extremities, and face. Laryngeal edema was present causing considerable difficulty in breathing, and a tracheotomy tray was placed at his bedside. He had had this condition for two days. Penicillin therapy had been given two weeks previously. His temperature was 101 F. Administration of diphenhydramine (benadryl®) hydrochloride in 100 mg. doses was ineffectual. Administration of epinephrine hydrochloride, 10 minims, gave only slight relief. Treatment with 100 mg. of diphenhydramine every four hours was continued with overlapping injections of epinephrine hydrochloride every four hours during the evening and night of admission. The patient's condition was the same on the second hospital day.

Corticotropin was administered on the second hospital day, 10 mg. every four hours in four injections to a total of 40 mg. The response was dramatic. The patient felt definitely better about an hour after the first injection; and shortly after the second injection all troublesome edema subsided, pruritus had disappeared, and the only complaint was a fairly marked residual weakness. The lesions cleared completely later in the day. No further treatment was received. There had been no recurrence by the thirteenth hospital day.

Comment.—Case 4 represents the dramatic response of an extremely severe and generalized, giant urticaria to 40 mg. corticotropin.

Case 6.—DWA, age 19, presented severe angioneurotic edema of the hands and feet and smaller lesions of the trunk of two days' duration. The condition had been gradually getting worse. He had a history of recent penicillin injections. There was no response to antihistaminic therapy. The feet, particularly, were severely involved, and the patient had trouble hobbling around.

Cortisone was administered in a 25-mg. dose every three hours four times to a total of 100 mg. The patient complained of joint pains during the cortisone therapy, but this subsided shortly after completion and did not recur. There was no further treatment. The edema subsided gradually and was gone on the second hospital day. There was occasional mild pruritus on the second

hospital day, but it was entirely gone by the third hospital day. On the third day the feet and hands showed a slight erythema, but no actual edema. There were no symptoms by the fourth hospital day. There had been no recurrence two weeks later.

Comment.—In Case 6 an angioneurotic edema (penicillin) had good response to 100 mg. cortisone.

CASE 9.—JEB, age 37, presented marked edema and swelling of the face, eyelids, hands, and feet, and extensive urticarial lesions over the trunk and extremities of two days' duration. He had had penicillin therapy 10 days previously. There was little relief from calamine lotion administered locally and antihistaminics. On the first hospital day he was given 20 mg. of corticotropin twice without benefit. On the second hospital day he was given 50 mg. diphenhydramine hydrochloride and 10 cc. of calcium gluconate, both intravenously. There was prompt relief of the pruritus with only minimal symptoms. The relief lasted for about three hours with no change in the appearance of the lesions. In the afternoon 100 mg. of diphenhydramine hydrochloride was administered orally, 10 cc. of calcium gluconate intravenously, and 20 mg. of corticotropin. The patient was comfortable, and edema and urticarial lesions were nearly gone by evening. On the third hospital day there was continued improvement of the lesions, and only mild pruritus was present. Tripelennamine (pyribenzamine®) hydrochloride in a 50-mg. dose was administered twice for pruritus. On the fourth hospital day all treatment was discontinued. On the fifth day the patient had a few transient erythematous lesions which disappeared with no therapy. On the sixth hospital day there were no symptoms, and the lesions had completely disappeared. On the tenth hospital day there had been no recurrence except transient swelling of the right knee one day.

Comment.—In Case 9 a patient with penicillin urticaria showed poor response to corticotropin; good response to antihistaminics combined with intravenously injected calcium, with a relapse in three hours, and good response to a combination of antihistaminics, intravenous administration of calcium gluconate, and corticotropin.

CHRONIC URTICARIA

The method of treatment of chronic urticaria was, in general, much the same as that used in acute urticaria. There were five patients with chronic urticaria, durations of which varied from one and one-half months to over five years. The results in the patients with chronic urticaria were disappointing. Only one of the five showed any response to corticotropin or cortisone. One patient showed prompt response to corticotropin, but the lesions recurred one week after treatment. The case of one patient (Case 19) was interesting in that he failed to respond to either corticotropin or cortisone; but given antihistaminics, combined with intravenous injections of calcium gluconate, he became symptom free for the first time in 18 months. He remained free during the one week of treatment and the first post-treatment week. He then developed mild recurrent pruritus which required no treatment and seemed to be subsiding.

None of the chronic cases was definitely due to penicillin, although it was apparent from remarks overheard in the ward that one of the "cause-undetermined" patients had been using penicillin prophylactically.

The data on the chronic urticarial cases are presented in summary form in Table 2.

REPORT OF CASES

CASE 16.—OA, age 33, had a marked urticaria of four months' duration, which developed the day following a tetanus-toxcid injection. A multitude of treatment had been of no benefit. He had tried from time to time to return to work but had only remained a day or two on each occa-

sion. He had had no real benefit from calcium gluconate given intravenously, ascorbic acid, antihistaminics, or epinephrine hydrochloride. On the first hospital day 20 mg. of corticotropin was administered four times to a total of 80 mg. There was about 75% improvement in the pruritus by the second day, but the urticarial lesions remained as before. Diphenhydramine hydrochloride was administered for residual pruritus. On the third hospital day the pruritus had subsided, and all lesions had disappeared. Treatment with diphenhydramine hydrochloride was discontinued on the fifth hospital day. There were no further symptoms and the patient was discharged on the seventh hospital day.

The patient was admitted again 18 days later. He had returned to work, but the urticarial lesions had recurred in about one week's time and had become increasingly worse. On the first hospital day 10 mg. of corticotropin was administered four times. On the second hospital day the urticarial lesions had disappeared, but a moderate pruritus was present. Cortisone was administered in a 25-mg. dose, four times. The urticaria and pruritus became worse during

TABLE 2.—*Summary of Data on Chronic Urticaria*

Case No.	Name, Age	Diagnosis	Response to: Corticotropin	Response to: Cortisone	Response to: Antihistaminics with Calcium Gluconate*	Comment
16	OA, 33	Urticaria, severe, 4-mo. duration; tetanus toxoid injection	A	c	ah	H-1, ACTH 20 mg. × 4 (80 mg.); good response; recurrence 1 wk. later (Second admission) H-1, ACTH 10 mg. × 4 (40 mg.); fair response H-2, cortisone 25 mg. × 4 (100 mg.); became worse H-3, ACTH 10 mg. × 4 (40 mg.); good response; recurrence in 8 days H-11, antihistaminics with calcium gluconate
17	BFW, 22	Urticaria, 4-mo. duration; cause undetermined	a	c	..	H-1, ACTH 10 mg. × 4 (40 mg.) H-2, H-3, H-4, cortisone 25 mg. × 4 (100 mg. daily)
18	ERS, 22	Angioneurotic edema, 1½-mo. duration; cause undetermined	a	c	ah	H-10 and H-11, ACTH 10 mg. × 4 (40 mg. daily) H-14, cortisone 25 mg. × 4 (100 mg.) H-15, cortisone 100 mg. × 2 (200 mg.) H-25 through H-28, antihistaminics with calcium gluconate
19	DSP, 36	Urticaria, 18-mo. duration; amebiasis and hepatitis	a	c	AH	H-1, ACTH 10 mg. × 4 (40 mg.) H-2, H-3, H-4, cortisone 100 mg. × 2 (200 mg. daily) H-14 through H-20, antihistaminics with calcium gluconate; symptom free for first time in 18 mo.; mild recurrence 1 wk. later
20	LJW, 25	Urticaria, 5-yr. duration; cause undetermined	a	c	..	H-1, ACTH 10 mg. × 4 (40 mg.) H-2 and H-3, cortisone 100 mg. × 2 (200 mg. daily)

* Antihistamine dosage was 100 mg. orally every 6 hr. concurrent with 1 gm. calcium gluconate intravenously twice daily.
Key to symbols: A, good response to ACTH; a, poor response to ACTH; C, good response to cortisone; c, poor response to cortisone; AH, good response to antihistaminics with calcium gluconate; ah, poor response to antihistaminics with calcium gluconate; H-1, first hospital day, etc.

cortisone treatment. On the third hospital day 10 mg. of corticotropin was administered four times. There was definite improvement. On the fourth hospital day all pruritus and urticaria had cleared.

There was a recurrence on the eleventh hospital day. The lesions were not as marked as previously, although pruritus was still troublesome. No particular benefit was derived from antihistaminics given together with intravenous calcium gluconate.

Comment.—In Case 16 a patient with severe urticaria due to tetanus toxoid had good response to one day's treatment with corticotropin but had a recurrence about one week later. There was poor response to cortisone and poor response to antihistaminics with intravenous injections of calcium gluconate.

CASE 19.—DSP, age 36, presented chronic recurrent urticaria of one and one-half year's duration, secondary to a chronic amebiasis and hepatitis. There was no further evidence of active amebiasis. Residual mild hepatitis was present. The urticaria was not severe but sufficient

to cause discomfort from pruritus. There were fleeting associated joint pains, although no definite joint swelling. Mild dermographism was present. Corticotropin, 10 mg., was administered four times on the first hospital day without benefit. Cortisone, in a 100-mg. dose, was administered twice daily on the second, third, and fourth hospital days without benefit. On the fourteenth hospital day a course of diphenhydramine hydrochloride administered orally was begun in a dosage of 100 mg. four times daily, with calcium gluconate injections twice daily, and this treatment was continued daily for one week. There was complete freedom of lesions and symptoms during this week. This was the first time in 18 months that the patient had remained free of pruritus. There was no recurrence one week later, but the following week the patient had a mild recurrence. No treatment was given, and the lesions seemed to be subsiding over a 10-day period.

Comment.—In Case 19 a chronic urticaria due to amebiasis and hepatitis showed poor response to corticotropin and cortisone but good response to diphenhydramine hydrochloride with intravenous injection of calcium gluconate.

TABLE 3.—*Summary of Data on Miscellaneous Allergic Dermatoses*

Case No.	Name, Age	Diagnosis	Response to: Cortico-tropin	Response to: Corti-sone	Comment
21	HPL, 28	Dermatitis venenata (plants)	A	..	H-1, ACTH 20 mg. × 4 (80 mg.); prompt relief of edema and symptoms, no definite shortening of healing time
22	WVH, 20	Dermatitis venenata (poison oak)	a	..	H-1, ACTH 20 mg. × 1 (total dose)
23	JLK, 20	Dermatitis venenata (poison oak)	..	c	H-1, cortisone 25 mg. × 4 (100 mg.)
24	RLB, 20	Dermatitis venenata (poison oak)	..	C	H-2, cortisone 50 mg. × 2 (100 mg.); prompt relief of symptoms, dermatitis itself responded in about normal time
25	CAR, 23	Dermatitis venenata (laboratory chemicals)	..	C	H-2, cortisone 25 mg. × 4 (100 mg.); definite relief of symptoms, no definite shortening of healing time
26	CDP, 26	Atopic dermatitis (mild)	..	c	H-1, cortisone 25 mg. × 4 (100 mg.) H-2, cortisone 50 mg. × 4 (200 mg.) H-3 through H-9, cortisone 25 mg. × 2 (50 mg. daily)
27	WNS, 20	Fungus "id" reaction	..	c	H-1, cortisone 50 mg. H-2, cortisone 100 mg.

Key to symbols: A, good response to ACTH; a, poor response to ACTH; C, good response to cortisone; c, poor response to cortisone; AH, good response to antihistaminics with intravenous calcium gluconate; ah, poor response to antihistaminics with intravenous calcium gluconate; H-1, first hospital day, etc.

MISCELLANEOUS CASES

Five cases of acute severe dermatitis venenata were included in the miscellaneous allergic dermatoses. The results were encouraging enough to warrant use of corticotropin or cortisone in more severe cases of this type. It is to be noted that, while relief of symptoms was usually prompt and the patient made comfortable, there was no marked shortening of the time required for complete healing of the dermatitis.

One patient with atopic dermatitis and one with allergic "id" were treated with cortisone with no benefit.

The case data are presented in summary form in Table 3.

SUMMARY AND CONCLUSIONS

Acute Urticaria.—Patients with acute urticaria showed a uniformly good response to corticotropin (ACTH) therapy. (Two patients did not, but the dosage was small.) On the basis of the cases presented, an optimum recommended

dosage is 10 mg. repeated every three hours, four times (total, 40 mg.). If there is no clinical response to the initial 10-mg. dose, an increase to 20-mg. dosage is recommended for the remainder of treatment. One day's treatment should be sufficient in most cases. Mild residual pruritus may be expected in some patients, but it usually subsides in two to three days, with or without antihistaminics.

Good response in patients with acute urticaria can usually be expected from cortisone, although it appeared to be less effective than corticotropin.

Antihistaminics used in conjunction with intravenous calcium gluconate were of definite but transient benefit to some patients with acute urticaria. They are not as beneficial as either corticotropin or cortisone in acute urticaria but have the advantage of being always available and inexpensive.

Chronic Urticaria.—Both corticotropin and cortisone in the short-dosage schedules used were disappointing in the treatment of chronic urticaria.

Antihistaminics with intravenous administration of calcium gluconate gave an excellent response in one patient who had failed to respond to corticotropin and cortisone.

Acute Dermatitis Venenata.—Results were encouraging enough to warrant the use of corticotropin or cortisone in the more severe cases. Definite shortening of the healing time cannot be expected, although prompt relief of symptoms can usually be anticipated.

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Clinical Notes

ANTIHISTAMINIC LOTION FOR MILIARIA

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Topical application of the antihistaminics has been practiced rather extensively during the past few years, especially when incorporated in ointment bases and as iontophoretic agents, as shown by Aaron, Peck, and Abramson.[1] The effectiveness of antihistaminics in ointment bases is certainly questioned on the basis of the work done by Perry.[2] It was our opinion that from a dermatological viewpoint such drugs, if effective, would be more satisfactorily used in a simple alcoholic lotion.

An effective treatment of miliaria has been a constant problem for the members of the armed forces serving in tropical countries, and though there are many paliative preparations in use, nothing has been found to be truly satisfactory. An example of a standard preparation for treatment of miliaria is salicylic acid 3%, glycerine 4%, phenol 1%, menthol .25%, and alcohol 95%. To this basic preparation three antihistaminics were added in turn: (1) diphenhydramine (benadryl,® Parke, Davis & Company), (2) tripelennamine (pyribenzamine,® Pharmaceutical Products, Inc.), and (3) methapyrilene hydrochloride (thenylene,® Roche-Organon, Inc.). Of the three,[3] diphenhydramine was most readily available at the time this work was done.[4] Diphenhydramine was added to the above basic preparation in a 2% concentration, and the resultant combination proved to be readily applicable.

For this experiment 200 subjects were used; the subjects were members of the armed forces serving in the Philippine Islands Command. To better evaluate the results and place the experiment on a comparative basis, patients were chosen who had a relatively similar degree of miliaria in so far as concerned (1) extensiveness of involvement, (2) severity, and (3) secondary infection. Patients were alternated as they reported on sick call, the even ones being given the basic preparation without diphenhydramine and the odd ones receiving the basic preparation with diphenhydramine (2%) added.

The subjects were instructed to apply the lotion three times daily; the lotion was to be applied by hand freely to all the involved areas. They were also instructed to bathe each evening and to make their last daily application following the shower bath. Each patient was examined daily and his progress charted. In no case was irritation as the result of the treatment noted, though occasional temporary smarting was remarked on.

It should be mentioned at this point that this experiment was carried out on patients who had mild to moderately severe miliaria. No patients with severe eczema were included. (No relief was noted in the one hospitalized patient with tropical anhidrotic asthenia, aside from the initial cooling effect of the preparation.) The subjects under consideration were kept on a full-duty status during the experiment. (No hospitalized patients were included with the

1. Aaron, T. H.; Peck, S. M., and Abramson, H. A.: Iontophoresis of Pyribenzamine Hydrochloride in Pruritic Dermatoses, J. Invest. Dermat. **10**:85, 1948.

2. Perry, D. J.: The Local Use of Benadryl Ointment, J. Invest. Dermat. **9**:95, 1947.

3. Sulzberger, M. B.; Baer, R. L., and Levin, H. B.: Local Therapy with Pyribenzamine Hydrochloride, J. Invest. Dermat. **10**:41, 1948.

4. This work was done in 1948 to 1949 in the Philippine Islands (10th General Hospital and 18th Medical Group).

exception of the one with tropical anhidrotic asthenia as noted, and this one was not considered in the series.) The results of this experiment are shown in the following table.

As can be noted, a similar degree of immediate relief was afforded with both preparations, but prolonged relief (30 min. plus) was seen only with the preparation to which diphenhydramine had been added. This diphenhydramine preparation did not show the side effects of vertigo, palpitation, anosmia, loss of taste sensation, or the eczematous contact-type dermatitis as reported by Sulzberger with 2% tripelennamine hydrochloride ointment.[3]

On questioning, all patients said they preferred the lotion to ointments and remarked on its ease of application. A few patients (17) complained that the preparation caused peeling of their palms, but stated that this feature was not bothersome. Each patient required an average of

Effect of Lotion Containing Diphenhydramine on Miliaria

Immediate Cooling Action	Basic Lotion with Benadryl® 100	Basic Lotion Without Benadryl® 100
Evidence of primary irritation or sensitization	0	0
Complete relief of pruritus beyond initial cooling (30 min. +)	61	18
Moderate relief of pruritus beyond initial cooling	36	21
No appreciable prolongation of antipruritic effect	3	61
Complete clearing of secondary infection in 48 hr	47	46
Definite improvement of secondary infection in 48 hr	43	42
No improvement of secondary infection in 48 hr	10	12

approximately 8 oz. (22.7 gm.) of the lotion during treatment for proper application. The average duration of treatment was five days. There were no complaints as concerns staining or damage to clothing.

From this study we have concluded that the basic alcoholic lotion which has been used in the treatment of miliaria can be much improved by the addition of 2% diphenhydramine.

80 162d St.

140 E. 54th St.

CONTACT DERMATITIS OF THE FACE DUE TO MATCHES

J. F. BURGESS, M.D., F.R.C.P.(C)
AND
R. ROY FORSEY, M.D., F.R.C.P.(C)
MONTREAL, CANADA

Match and match box dermatitis has been described by several authors.[1] Primary involvement is usually in the pocket area in which matches have been carried. In a few cases, there has been a secondary spread to involve the face. Recently we have seen two cases of dermatitis of the face not associated with lesions elsewhere. In these two cases, "strike anywhere" matches proved to be the offending contactants.

We wish to present these cases in order to draw attention to the fact that matches should be considered in unexplained cases of contact dermatitis of the face simulating nail polish dermatitis.

REPORT OF CASES

CASE 1.—Mrs. R. B., aged 60, had a frequently recurring contact dermatitis of the face for five years. The attacks were accompanied with erythema, irritability and edema, notably about the eyes, and lesions also occurred on the sides of the chin and neck. The whole picture reminded

1. (*a*) Eaton, W. E.: Dermatitis Produced by Matches, U. S. Nav. M. Bull. **11**:540, 1917. (*b*) Fox, G. H.: Match-Box Dermatitis, J. Cutan. Dis. **36**:530, 1918. (*c*) Rasch, C.: Dermatitis from Safety Matches, Ugesk. laeger **80**:258, 1918; (*d*) Match Box Dermatitis and Conjunctivitis, ibid. **98**:1119, 1921. (*e*) Foerster, D. H.: Match and Match-Box Dermatitis, J. A. M. A. **81**:1186 (Oct. 6) 1923. (*f*) Klauber, R.: Match and Match-Box Dermatitis, Brit. J. Dermat. **50**:451, 1938.

one of nail polish dermatitis. All possible irritants such as cosmetics were removed, and skin tests and other investigative procedures were carried out, without the causative factors being determined. The attacks usually necessitated confinement to bed for a few days, together with the use of wet compresses and antihistamine therapy.

A chance remark by the patient in March 1950 led to a consideration of the possibility that match ends were the cause of her condition. She was a moderate smoker and had usually used "strike anywhere" matches. A clue was given when she stated that she would give up smoking if it would help. A patch test with match ends was applied, and at the end of 36 hr. the area was raised, erythematous and mildly vesicular. Unlike many other patch reactions, this one did not subside immediately but was still present four weeks later. As soon as the use of "strike anywhere" matches was discontinued, no further eruption occurred, and the skin has remained entirely clear over the past year. Recently, there was a mild recurrence after the use of these matches.

Case 2.—Mr. S., a 40-yr.-old man had a contact type of dermatitis about the right ear and right eye, which spread to involve most of his face. The condition waxed and waned for a period of two months. An intensive search was made to eliminate all possible sensitizers. The history revealed a flare-up of the disease on week ends while he was at home. An acute eruption also developed in the middle of the week during a business conference in New York. At that time, two months after the onset of the eruption on the face, a patch appeared on the right thigh beneath the patient's side pocket. We then discovered that he used "strike anywhere" matches at his home on week ends and that he had used them while away on his business trip. At his office, he used a table lighter. A match head was applied to the skin on the forearm, and within four hours a strongly positive reaction developed. The eruption entirely subsided as soon as he discontinued using matches, and the skin has remained clear until the present time (four months later).

The offending agent in the match head is apparently phosphorus sesquisulfide (P_4S_3).[1f]

SUMMARY

Two cases of recurring dermatitis of the face due to indirect contact with "strike anywhere" matches have been presented.

1414 Drummond Street.

SINUS TRACT OF DENTAL ORIGIN

OTIS FIELD JILLSON, M.D.
AND
ROBERT H. PRESTON, M.D.
HANOVER, N. H.

Sutton and Sutton [1] state that the rarely mentioned sinus tract of dental origin can lead to an asymptomatic cold abscess which eventually ruptures through the skin. Because of gravitational forces, the fistula usually terminates on the chin. Anderson,[2] in a complete review of the subject, cites the fact that the cutaneous findings may simulate actinomycosis or granuloma pyogenicum.

Fellow in Dermatology (Dr. Preston).

From the Department of Dermatology, Dartmouth Medical School and Hitchcock Clinic.

1. Sutton, R. L., and Sutton, R. L., Jr.: Diseases of the Skin, ed. 10, St. Louis, C. V. Mosby Company, 1939, p. 1490.

2. Anderson, P.: Persistent Sinus Tracts of Dental Origin, Arch. Dermat. & Syph. **35**:1062 (June) 1947.

REPORT OF A CASE

Mr. J. D., 24 yr. old, was first seen on Nov. 14, 1949, with a granuloma pyogenicum located on the midaspect of the chin (Fig. 1). It had persisted for eight months despite repeated electrocoagulation, antibiotics, and radiation. Past history revealed that the patient had received a blow on the chin during a fight a year previously.

Fig. 1.—Fistula opening on chin after removal of granuloma pyogenicum.

Fig. 2.—Apical abscess surrounding two lower incisors.

On physical examination, no obvious dental defects were found, but roentgenograms demonstrated a large apical abscess surrounding the two lower incisors (Fig. 2). After extraction of these two incisors, with curettage of the abscess cavity, the fistula promptly healed, without recurrence. (A probe was extended from the mouth out through the fistula opening on the chin.)

SUMMARY

Another case of sinus tract of dental origin simulating granuloma pyogenicum is reported. Cure resulted only when the dental disease was found and eradicated.

TREATMENT OF FOLLICULITIS KELOIDALIS CHRONICA NUCHEA (ACNE KELOID)

LESTER HOLLANDER, M.D.
PITTSBURGH

The infrequently encountered, specifically localized, extremely chronic disease located on the back of the neck was described in 1869 by Kaposi and called dermatitis papillaris capillitii. In 1874 Bazin named it acne keloid, and in 1895 Ehrmann suggested the name folliculitis (sycosis) nuchea sclerotisans. In 1939 Sutton and Sutton and in 1946 Andrews classified it as folliculitis keloidalis; most dermatologists refer to it as acne keloid. I think the name folliculitis keloidalis chronica nuchea, though lengthy, is the most appropriate.

MacKenna [1] too considered it an unfortunately named variety of folliculitis, since it is neither an acne nor a keloid in any true sense. He described it as consisting of a longitudinal band of chronically inflamed follicles, situated on the back of the neck, usually some distance below the margin of the scalp hair. He continued: "The surface and edges of this band are rugged to the eye and hard to the touch. The lesion bears some resemblance to a low-lying rock barrier emerging from the sea."

MacLeod and Muende [2] in a less picturesque language stated, "Hypertrophy of the connective tissue not infrequently occurs in association with acneiform lesions. A peculiar disease, in which they are invariably concomitant, has been described under the heading acne keloid. In this disease hypertrophic scar tissue develops round a deep seated peri-follicular abscess. Clinically, the lesions appear as nodules, which are dotted over with pustules and hair tufts and are generally situated about the neck."

There are a few other characteristics which may be added. 1. It is a very chronic and extremely slow but progressive disease. Its full development entails several years, but when it reaches an extent which may be termed its zenith, it becomes stationary, and in that sense it is a self-limited disease. 2. It occurs almost exclusively in young men. Its activity is most pronounced during their third decade. This is in agreement with Highman,[3] who contended that acne keloid is a disease of males, and also with Molesworth,[4] who stated that acne keloid occurs only in men. 3. Cases of the disease in five women reported by various authorities have not been accepted as true examples of this disease by Galewsky, as stated by McCarthy,[5] though he had seen this disease in two young Negro females. 4. The subjects have kinky, curly, or thick-shafted hair. Sequeira [6] wrote that, although acne keloid is a rare disease in his experience, Castellani had said that the disease is common in native races. Knowles [7] was also of the opinion that it occurs particularly in adult male Negroes. 5. It is an infrequent disease except in Negro men. Hazen [8] stated that among whites it is extremely rare, but in Negroes it forms nearly 0.5% of dermatologic cases.

I have treated six private patients since 1940 who had advanced forms of this disease; of these, three were Negro, two were Italian, and one was a white American. All were young men in their twenties.

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1. MacKenna, R. W.: Diseases of the Skin: A Manual for Students and Practitioners, ed. 3, Baltimore, William Wood & Company, 1933, pp. 55-56.

2. Macleod, J. M. H., and Muende, I.: Practical Handbook of the Pathology of the Skin, ed. 2, New York, Paul B. Hoeber, Inc., 1940, pp. 236-237.

3. Highman, W. J.: Dermatology: The Essentials of Cutaneous Medicine, New York, The Macmillan Company, 1921, p. 368.

4. Molesworth, E. H.: An Introduction to Dermatology, London, J. & A. Churchill, Ltd., 1937, p. 111.

5. McCarthy, L.: Diagnosis and Treatment of Diseases of the Hair, St. Louis, C. V. Mosby Company, 1940, p. 299.

6. Sequeira, J. H.: Diseases of the Skin, ed. 4, New York, The Macmillan Company, 1927, p. 217.

7. Knowles, F. C.: Diseases of the Skin, ed. 2, Philadelphia, Lea & Febiger, 1923, p. 540.

8. Hazen, H. H.: Diseases of the Skin, ed. 3, St. Louis, C. V. Mosby Company, 1927, p. 512.

The treatment with x-rays, as advocated by MacKee,[9] even when it was combined with the use of repeated freezing with solid carbon dioxide[10] and repeated electrodesiccation, was unsatisfactory in the first three of these six patients.

The fourth patient was treated with electrodesiccation and daily injections of penicillin for a period of two weeks. He was subjected to four such courses of treatment; finally, since the disease persisted, the treatment was discontinued, and I lost track of the patient.

The last two patients have been treated with massive electrodesiccation on two separate occasions at two-month intervals, and in addition they were instructed to ingest 10 mg. of diethylstilbestrol morning and night. The later treatment was continued for a total period of eight months. Surprisingly no mastodynia developed. These two patients have shown and maintained a satisfactory improvement. The time elapsed has been 10 mo. since the last electrodesiccation of either patient, and, although some transverse thickening and a permanent alopecia exists at the previously involved site, there seems to be no recurrence of the disease itself.

TREATMENT IN DETAIL

Description of the treatment with massive electrodesiccation follows. 1. A large area of the adjacent and unaffected scalp is shaved and washed with soap and water, then sponged with alcohol. 2. By use of a pressure syringe, 10 to 20 cc. of 2% procaine hydrochloride and epinephrine, 1:25,000 solution, is injected at eight points surrounding the involved area. The point of the needle is directed toward and under the keloidal mass. Considerable pressure is necessary to introduce the anesthetic solution. 3. A 10-min. waiting period is observed, to give the anesthetic an opportunity to take full effect. 4. By use of a unipolar electrodesiccating needle, as much of the keloidal structure as possible is destroyed. 5. The accumulation of heat often causes discomfort during the treatment. Therefore it is essential that the electrodesiccation be stopped for a cooling-off period of two to three minutes at a time. 6. All of the charred tissue is removed with a pair of curved scissors; care is exercised to avoid cutting into the undesiccated tissue. 7. The electrodesiccation is considered completed when a trench of 1 to 1.5 cm. in depth is reached and when no palpable fibrous tissue is discerned. 8. A 3%-aureomycin-hydrochloride-ointment dressing is applied. 9. The wound is similarly dressed every third day until healing is completed. This usually takes about three weeks. 10. This electrodesiccation has to be repeated at two month intervals, because some of the keloid regrows.

Since this disease is encountered almost exclusively in young male adults and only rarely if ever (McCarthy's cases excluded) in young women, it seemed reasonable to try an addition of diethylstilbestrol to this treatment; consequently diethylstilbestrol in 10-mg. doses twice a day was ordered ingested for a total period of eight months.

It is probable, though purely speculative, that the earlier in the course of the disease this treatment is employed, the greater the likelihood there is of its success.

631 Jenkins Bldg.

9. MacKee, G. M.: X-rays and Radium in the Treatment of Diseases of the Skin, ed. 3, Philadelphia, Lea & Febiger, 1938, p. 669.

10. Sutton, R. L., and Sutton, R. L., Jr.: Diseases of the Skin, ed. 10, St. Louis, C. V. Mosby Company, 1939, p. 1417.

ALLERGIC STOMATITIS DUE TO "BAXIN" IN A DENTIFRICE

ALEXANDER A. FISHER, M.D.
WOODSIDE, N. Y.
AND
MAXWELL LIPTON, M.D.
ASTORIA, N. Y.

"Baxin" is an antiseptic which has recently been added to some soaps and tooth pastes. Chemically, "baxin" is dichlorodihydroxydiphenylmethane and is closely related to the trichloro compounds which have received considerable attention in dermatologic circles under the designation of G-11.

Information about "baxin" and a supply for clinical testing was furnished by Arnold J. Singer, Ph.D., Director of Research, Amm-I-Dent, Inc., Jersey City, N. J.

A search of the literature has revealed no report of stomatitis or dermatitis due to "baxin." Since the use of "baxin" seems to be increasing, we feel that it is well worth while to report a case of allergic stomatitis which simulated a vitamin-B deficiency.

REPORT OF A CASE

One of us (M. L.), aged 53, began to complain of a burning sensation of the mouth in January, 1951. The tongue became cherry-red, glazed, and swollen. There was a sensation of numbness and a marked loss of sense of taste. The lips became dry and slightly scaly, and fissures appeared at the angles of the mouth.

An internist suggested the possibility of a vitamin-B-deficiency syndrome. Administration of vitamin B complex and added riboflavin, both orally and by intramuscular injection, caused no improvement.

The symptoms became steadily worse over a period of two months, in spite of all forms of therapy, and mastication became increasingly difficult.

A careful history then revealed that the onset of the symptoms coincided with the use of a new ammoniated tooth paste. It was noted that this tooth paste contained "baxin." As soon as the patient stopped using the tooth paste the stomatitis cleared in 24 hr.

Patch tests with five different ammoniated tooth pastes not containing "baxin" were applied to the upper arm. Results were negative. A patch test with the tooth paste containing "baxin" gave a positive reaction after 48 hr. in the form of fine vesicles. Ten control patients gave no reaction to patch tests with the "baxin"-containing tooth paste. Since "baxin" is insoluble in water, a 5%-"baxin"-petrolatum ointment was made and applied to 10 control patients as patch tests. All reactions were negative after 48 hr. The reaction to the 5%-"baxin"-petrolatum mixture was positive after 48 hr. on the patient with stomatitis. Use of the "baxin"-containing tooth paste caused a recurrence of the symptoms within two hours.

SUMMARY

A "baxin"-containing ammoniated tooth paste was found to be the cause of a stomatitis, glossitis, cheilitis, and perlèche resembling a vitamin-B deficiency.

Reactions to patch tests with the tooth paste and a 5%-baxin"-petrolatum mixture were positive on the patient and negative on 10 normal controls.

In addition, avoidance of the "baxin" tooth paste brought prompt cessation of symptoms. After all symptoms had ceased for two months, use of the "baxin" tooth paste caused prompt recurrence of the symptoms and signs. Thus the "baxin" was incriminated both clinically by use and experimentally by patch-testing.

45-14 48th St.

30-74 36th St.

PREPARATION OF SLUSH

GARRETT A. COOPER, M.D.
AND
CHARLES W. STOOPS, M.D.
MADISON, WIS.

Carbon dioxide slush (solidified carbon dioxide-acetone-sulfur mixture) has many uses in dermatology. The preparation of this material is time-consuming and tedious. The difficulty in preparing the slush lies in breaking up the carbon dioxide slabs into a fine powder. Rather than pulverize this material by hand, we have been using an ordinary kitchen meat grinder (Universal No. 1). The slabs of solidified carbon dioxide are cracked into small pieces (4 to 5 cm. in size), which are placed in the meat grinder and pulverized in the usual manner.

There are two advantages to this method. The material is of uniform size and the time of the pulverizing procedure is greatly reduced. After the solidified carbon dioxide is powdered, it can then quickly be made into slush in the usual method. We use a mortar and pestle, adding sulfur powder and acetone to reach the correct consistency as desired.

STRYKER FRAME IN TREATMENT OF PEMPHIGUS

PARASKEVAS MICHAELIDES, M.D.
AND
MILTON REISCH, M.D.
NEW YORK

Handling a patient bedridden with pemphigus always poses great medical as well as nursing problems. The use of the Stryker frame [1] offers a solution to a few of these problems.

The Stryker frame is used by surgeons for paraplegics, for treatment of patients with pelvic and intertrochanteric fractures, tuberculosis of the spine, and severe burns, and in general for patients who have an extensive osseous pathologic condition and who tolerate manipulation poorly.[2] The patient is turned, dressed, and attended in regard to bowel and urine habits without the lifting, pushing, and moving required in a regular bed. Movements of patients in this frame are minimal.

Photographs are presented showing the patient in the posterior frame (Fig. 1), the patient in the anterior frame (Fig. 2), and the frame itself (Fig. 3). The frame consists of an overhead

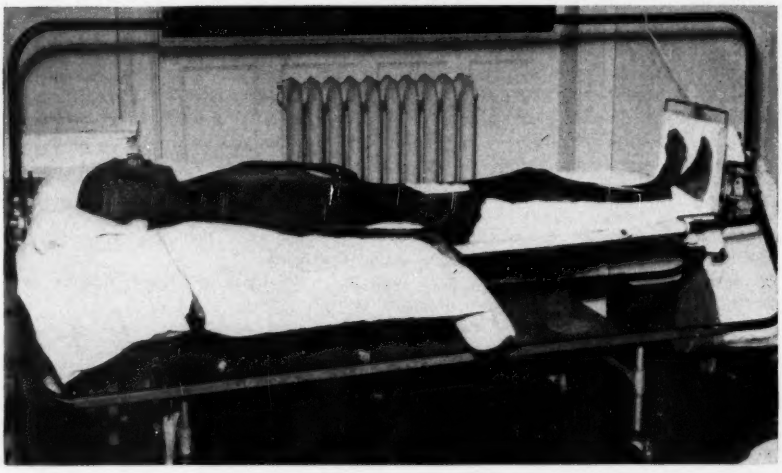

Fig. 1.—Patient in anterior frame.

bar (*A*) which is used for support of bed covers, an anterior frame (*B*) on which the patient lies face down, a posterior frame (*C*) on which the patient lies face up, a turning assembly (*D*) which permits rotation of the frames, and a wheeled cart (*E*) on which the frame rests. The frame upon which the patient lies is well padded. To turn the patient all that is necessary is to supply the upper frame with padding, forming a "sandwich" with the patient in the center;

From the Section of Dermatology and Syphilology, Medical Service, Veterans Administration Hospital.

Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the results of their own studies and do not necessarily reflect the opinion or policy of the Veterans Administration.

1. The Stryker frame is produced by the Orthopedic Frame Company, Kalamazoo, Mich.

2. Skinner, G.: Nursing Care of a Patient in a Stryker Frame, Am. J. Nursing **46:** 1 (May) 1946.

then the turning assembly is unlocked, the entire "sandwich" is turned over, and the top frame, which was at the bottom before turning, can then be removed. This entire procedure can be performed easily by a single person.

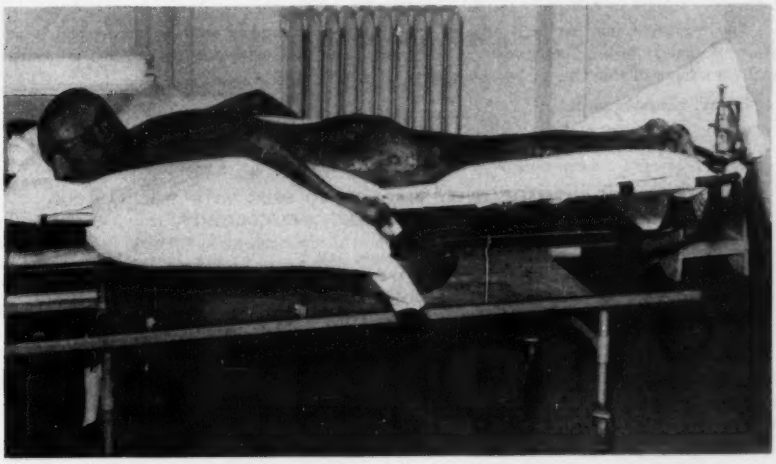

Fig. 2.—Patient in posterior frame.

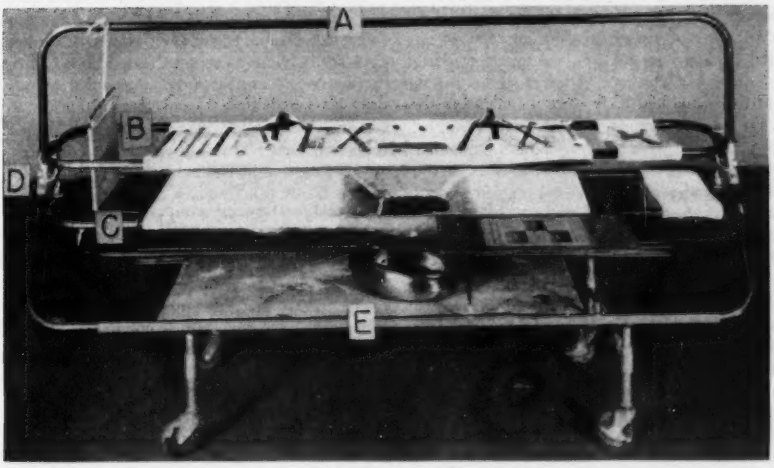

Fig. 3.—Stryker frame.

This type of bed has allowed us to handle patients with severe pemphigus, on whom the slightest trauma produced marked denudation, with a minimum amount of injury to the skin. As a result, we have been able to turn patients frequently, as often as every two hours in some cases, and thus have minimized the danger of hypostatic pneumonia. Covers are supported by the overhead bar and do not come in contact with the skin, thus avoiding another source

of trauma. The entire bed can be wheeled to the bathroom when medicated baths are indicated, again reducing the amount of movement imposed on the patient. With proper padding the incidence of decubitus ulcers has been diminished.

SUMMARY

The Stryker frame has been used in the treatment of patients with severe pemphigus in place of regular beds. Photographs of the frame, with and without a patient, are presented and advantages of this type of bed are given.

130 W. Kingsbridge Rd.

PREVENTION OF HYPERSENSITIVITY REACTION TO DRUG WITH SIMULTANEOUS ADMINISTRATION OF THE DRUG AND CORTONE®

LEON GOLDMAN, M.D.
AND
EVELYN ROCKWELL, M.D.
CINCINNATI

There are instances in which continuing use of a drug to which a patient is hypersensitive may be desirable and even necessary. Simultaneous administration of cortisone (cortone®)[1] may make this possible, as is illustrated by the following case. Cortisone and corticotropin (adrenocorticotropic hormone) are known to be of value in the treatment of drug eruptions.

REPORT OF A CASE

L. R., a 47-yr.-old male Negro, was admitted to the Dermatology Service at Cincinnati General Hospital on Jan. 8, 1951, with a seven-day history of sore lips and penis, fever and chills, loss of appetite, and headache. A proprietary medication (666 for colds®) containing 60 grains (3.9 gm.) of antipyrine was ingested 10 days before admission. Admission temperature was 102 F., and both his lips and anterior portion of the penis were edematous and denuded, with crusting and bleeding. Ulcerations of the buccal mucosa and erythematous, pigmented lesions on the hands and body were noted. After three days his temperature became normal and in 10 days he was asymptomatic. To prove the hypersensitivity to antipyrine, 3 grains (0.2 gm.) of antipyrine were given by mouth on January 20. The patient responded with a fever for four days, the temperature rising to 104.7 F. on the second day, severe abdominal pain, and pruritus of the perianal region and in the pigmented lesions on the hands. On January 27, after the patient was again asymptomatic, 100 mg. of cortisone were given at 2:00 and 4:00 p. m. Three grains (0.2 gm.) of antipyrine were given at 5:00 p. m. and another 50 mg. of cortisone at 5:30 p. m. No reaction, except minimal pruritus of the hands lasting only two hours, resulted.

In the above case, hypersensitivity to antipyrine was first proved by a flare-up reaction. Then this reaction was prevented by administering 200 mg. of cortisone prior to and 50 mg. shortly after a known-reaction dose of antipyrine. No experiments were done to determine the duration of protection after this schedule or to establish the level of the minimal protective dose of cortisone.

From the Department of Dermatology and Syphilology of the University of Cincinnati College of Medicine, Dr. Leon Goldman, Director.

1. Cortone® was supplied by Dr. J. M. Carlisle, Merck & Company, Inc.

Society Transactions

BRONX DERMATOLOGICAL SOCIETY

Charles R. Rein, M.D., Vice-President, in the Chair

Henry Silver, M.D., Secretary

Nov. 16, 1949

Treatment of Chloasma with Monobenzyl Ether of Hydroquinone. Presented by DR. ALEXANDER A. FISHER.

M. F., a woman aged 32, has had a variety of treatment for chloasma, which included solid carbon dioxide, hydrogen peroxide, alcoholic solution of mercury bichloride, strong alkaline soaps, and salicylic acid in alcohol.

On June 2, 1949 she began using 2% monobenzyl ether of hydroquinone in "laviderm." Fifteen days later an allergic contact-type eczematous eruption appeared in the areas where the ointment was rubbed in.

Reaction to patch tests with the above ointment and a 2% aqueous solution of monobenzyl ether of hydroquinone were strongly positive. Reaction to a patch test with "laviderm" was negative.

There was no apparent improvement in the chloasma after the contact dermatitis cleared.

DISCUSSION

DR. MARION B. SULZBERGER: Many years ago, when the first reports came out on loss of pigment from Age Rite Alba in rubber gloves, Dr. Ludwig Schwarzchild and I made many tests on persons domiciled in a city institution. Our object was to find out whether monobenzyl could be used as a means of producing deliberate therapeutic reduction or elimination of melanin pigmentation. These persons were mainly Negroes, but some white persons also volunteered. There was great irregularity in results obtained. Some became sensitized, and an eczematous allergic contact dermatitis developed, with no depigmentation; a few got depigmentation with no noticeable or significant preceding clinical dermatitis. In many there was no depigmentation or dermatitis, and some had both dermatitis and depigmentation. Our conclusions were that this chemical could not be used as a therapeutic agent under present conditions.

DR. JULIUS H. POLLOCK: I think that Dr. Fisher might want to modify the impression that this case is a failure. Unfortunately, a dermatitis developed in the patient, and, as has been pointed out by Dr. L. Schwartz, two weeks is not sufficient time to look forward to any pigmentary changes (ARCH. DERMAT. & SYPH. **42**:993 [Dec.] 1940).

DR. JOSEPH L. MORSE: In a personal communication Dr. Louis Schwartz stated that in everyone who came in contact with monobenzyl ether of hydroquinone depigmentation of the skin would develop sooner or later in the areas of contact. Does leucoderma develop only from contact, or can it occur in other areas from absorption of the hydroquinone through the skin?

DR. FRANZ HERRMANN: With regard to the effect of this substance on the pigmentation in skin areas distant from the site of the original contact, it appears possible that traces of the dry (powdered) material may reach such areas from the outside and be active through solution in the waxes of the skin surface, because of their high degree of liposolubility.

DR. PERRY M. SACHS: In a series of cases showing pigmentary disturbance following exposure to monobenzyl ether of hydroquinone, reported by Dr. E. Bernstein and me, the patients claimed and showed depigmentation in areas not limited to sites of direct contact (ARCH. DERMAT. & SYPH. **59**:542 [May] 1949). It is difficult to say whether these areas were involved secondarily by absorption or were indirect sites of contact. It is almost impossible to eliminate the latter possibility.

DR. ALEXANDER A. FISHER: I agree with Dr. Pollock that two weeks is not sufficient time for a fair trial, but the other patient was under treatment for four months without showing any change.

Multiple Simultaneous Anomalies of the Hair. Presented by DR. MORRIS LEIDER.

N. T., a housewife aged 39, complains of short and brittle hair of the scalp. The affection began about one year ago and followed the birth of twins. This is the third episode of the same condition, according to the patient. The first symptom occurred 30 years ago, at the age of 9 years, after an attack of influenza (epidemic of 1917). At that time the hair became short during convalescence and remained so for about six months. There followed gradual restoration to normal. The second episode occurred 17 years ago after an attack of pleurisy. On this occasion the hair again became short and remained so for about a year, after which it regained its usual character, again without any medical intervention. Another pregnancy several years ago was not attended by a relapse of the hair condition.

Examination in May, 1949, showed a full head of coarse hairs that were short and uneven in length (1 to 2 in. [3 to 8 cm.], in the main). The color of the hair was of several shades. The longest, which the patient stated were the most normal for her, were reddish (bronze, copper). The next longest were whitish, and the shortest were brunette. The reddish and brunette hairs appeared grossly normal; the whitish ones were clearly ringed. Variation in thickness of individual hairs could not be detected macroscopically. The eyebrows were short and a little ragged. On the tip and wings of the nose, the pilosebaceous orifices appeared plugged with comedo-like structures, which, however, showed a fuzzier surface than comedones usually present.

Microscopic examination of the hair of the scalp showed, particularly in whitish hairs, the characteristic alternation of dark spots or streaks and clear areas which accounts for the gross appearance of ring-forms. Some brunette hairs showed some degree of this phenomenon. In both whitish and brunette hairs, particularly the latter, points of shredded rupture could be seen, with the characteristic dovetailing or brushing of the shredded ends. The fuzzy comedo-like structures from the nose revealed themselves to be tiny bundles or brushes of hairs in aggregates of 10 to 50 filaments surrounded by a common sheath.

The clinical diagnosis was pili annulati (ringed hair). The microscopic diagnoses were trichorrhexis nodosa, pili annulati, and trichostasis spinulosa.

It is of interest, also, that the daughter of the patient shows ringed hair, but no other changes.

DISCUSSION

DR. MORRIS LEIDER: The presence of pili annulati in both mother and daughter suggests that this condition is hereditary and gene determined. But only the mother has trichorrhexis nodosa and that not as a lifelong condition but as a third occurrence.

The patient has been under observation for about five months and is much better now. The hairs have grown two to three times their length when first seen. Treatment has, of course, not been specific and has consisted of topical stimulating ointments. Perhaps the best advice was treatment of the constant headdress in the form of a snug skull cap. This may have prevented the development of fractures.

If one may make a judgment of origin from this one case, trichorrhexis nodosa seems to result from a metabolic disturbance precipitated by debilitating illness. During such crises the cellular columns that make up the hair strand seem to lack cemented solidity, which causes them to separate and fracture in the characteristic bush fashion. Some textbooks stress a traumatic factor and suggest that the entire picture is a result of mechanical injury from combing or other habits akin to trichotillomania. I doubt that any amount of mechanical abuse of normal hair can cause the appearance of trichorrhexis nodosa. Some claim to have found the condition in old and well-used shaving brushes. It so happened that when I received this case I had a shaving brush which had served me for 10 years and participated in about 3,500 shaves. Microscopic examination of its hairs showed that they were finely tapered, never fractured in the

striking dovetailed fashion of trichorrhexis nodosa. I am forced to the conclusion from my own experiments either that such observations were mistaken or that some persons were unfortunate enough to procure shaving brushes made from the hairs of badgers afflicted with trichorrhexis nodosa.

One other interesting observation was made in this case. It was found that hairs could be identified which would show the microscopic appearance of the characteristic fracture. Any hair that had a sharp bend in it would show the phenomenon under magnification. Moreover, such a hair could be made to show more fractures anywhere along its shaft if it were again sharply bent, then straightened and examined. At the point of the new bending a new fracture could be demonstrated.

Ragweed Dermatitis Successfully Treated with Oral Hyposensitization. Presented by DR. ALEXANDER A. FISHER.

P. B., a man aged 67, was previously presented before this Society on Oct. 21, 1948. This is the third annual presentation of the patient who has had ragweed dermatitis for 13 years.

For the past three years he has been receiving oral hyposensitization with plant oleoresin in corn oil, made by the Graham Laboratories, Dallas, Texas, according to Shelmire's method.

After the first year of treatment he showed slight improvement. After the second year the improvement was considerable (about 70%). This year he is completely free of ragweed dermatitis.

DISCUSSION

DR. ALEXANDER A. FISHER: This patient has had the third year of oral treatment and is finally clinically cured. Reaction to patch tests, which were strongly positive originally, are now only slightly positive.

DR. FRANK E. CROSS: Since the patch-test reaction is still positive, although even slightly so, would it not be advisable to continue with the treatment?

DR. DAVID BLOOM: Is it not possible that the patient became desensitized spontaneously?

DR. RUDOLF L. BAER: I think that the result in this case is of practical importance. The freedom from dermatitis, in this case, is not likely to be a mere coincidence, but is probably the result of the hyposensitization therapy. Any results which are obtained in ragweed dermatitis apply just as well to dermatitis due to other plants, such as poison ivy dermatitis. Of course, there is a possibility that the ragweed oil fraction sensitization in this patient had run its course after 13 years; yet it would be quite a coincidence that just at the time when treatment is instituted the eruption should improve from year to year and then disappear entirely. Dr. Earl Osborne of Buffalo stated, in a discussion on this subject some weeks ago, that in a number of his patients it took three years of oral hyposensitization to bring about desensitization, i. e., at least clinical desensitization.

I think it a most unusual occurrence that the reaction to patch test in Dr. Fisher's patient became practically negative. In a series of patients in whom oral poison ivy hyposensitization was carried out by a group of dermatologists with an extract prepared by the Graham Laboratories, there was, I believe, not a single patient in whom the positive patch-test reaction became negative, even when the patient appeared to have developed clinical protection against the plant.

Important conclusions are to be drawn from Dr. Fisher's case. If treatment is at all warranted, it should be continued over a period of years. I do not think that one should try to hyposensitize patients with mild poison ivy sensitivity, especially when they can stay away from the causal agent. But in patients with marked sensitivity who cannot avoid exposure, hyposensitization should be carried out over a long period of time and with really potent extracts. The method one uses is also important. The one devised by Shelmire of oral administration of gradually increasing doses of the allergen, starting with small amounts, is the method of choice. I also think that the Graham extract is probably of more uniform potency than any of the others. As Howell has shown, when one takes the extracts prepared by various pharmaceutical houses and applies them to the skin as patch tests, some will produce absolutely no reaction and some

will produce a 4+ reaction. That means that the physician has no idea of what he is injecting. Even different ampules of extract made by the same manufacturer may vary in potency. So far as poison ivy extracts are concerned, the pharmaceutical industry has not kept up with progress in investigative work; for there is a method available now by which the biologic extracts of poison ivy and related plants can be standardized, namely, by comparing in animal or human skin a given biologic extract with a given concentration of 3 pentadecyl catechol. So far, none of the pharmaceutical companies have taken this opportunity for standardization of their poison ivy extracts.

DR. ALEXANDER A. FISHER: I have now 11 patients with ragweed dermatitis. In the shortest case, the condition was of six years' duration, in the longest, 40 years' duration. Patients seem to respond the same way: in the first year about 20% relief, in the second year about 60% relief. This is the first case in the third year. The idea of spontaneous relief occurred to me also. I have written to Dr. Shelmire inquiring how to determine whether we are actually getting desensitization from the therapy. Dr. Shelmire expressed the view that he had never seen a spontaneous cure in ragweed dermatitis. In answer to Dr. Cross, we expect to continue treatment of these patients with a maintenance dose, 12 drops twice a week, for an indefinite period.

A Case for Diagnosis (Lupus Erythematosus? Lymphoblastoma?). Presented by DR. CHARLES A. GREENHOUSE and DR. WILLIAM M. SISKIND.

A Case for Diagnosis (Erythema Multiforme Bullosum Hemorrhagicum?). Presented by DR. FRANCIS PASCHER.

A Case for Diagnosis (Unusual Pigmentation?). Presented by DR. HANS H. BIBERSTEIN.

A Case for Diagnosis (Granuloma Annulare?). Presented by DR. MARTIN V. BOARDMAN.

Lichen Sclerosus et Atrophicus. Presented by DR. DAVID B. BALLIN.

Epithelioma Simulating Seborrheic Dermatitis. Presented by DR. CHARLES WOLF.

CHICAGO DERMATOLOGICAL SOCIETY

Theodore Cornbleet, M.D., *President*

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Jan. 17, 1951

Lupus Vulgaris After Treatment. Presented by DR. THEODORE CORNBLEET, DR. DAVID COHEN, and (by invitation) DR. J. F. SICKLEY.

The patient is a 49-year-old white woman who states that she has had facial lesions for about 25 years. Since July, 1950, the lesions of the face have been "wet."

One month ago a dry cough developed, with pain in the left side of the chest. She also has had intermittent fever and occasionally has chilly sensations. She has had no night sweats and no hemoptysis. For the past month she has had a constant feeling of fatigue. She has lost 10 lb. (4.5 kg.) since June, 1950.

She has been dyspneic and orthopneic for the past three or four weeks.

Results of physical examination were as follows: blood pressure, 220/120; in the chest, crackling rales throughout both lung fields and a few in both bases; a left heart beat at the midclavicular line, with a rate of 120, and no murmurs. The skin shows large erythematous, scaling, irregular patches involving most of the face and part of the neck and scalp. There are a few isolated lesions of the arms. On the left mandible there is a large crusted area.

Laboratory findings were as follows: Results of urinalysis were normal. Hemoglobin was 89%; red blood cells, 4.69; white blood cells, 10,050; polymorphonuclear leucocytes 76, lymphocytes 8, eosinophils 4, and monocytes 12%. Reaction to serologic tests was negative. Total plasma protein was 7.2 gm. Blood calcium was 10.8 mg. per 100 cc., and nonprotein nitrogen, 34. The electrocardiogram was normal. Sputum smears were negative for acid-fast bacilli. Results of sputum culture have not been reported yet. Findings from a roentgenogram of the chest were compatible with the miliary acid-fast process. Bronchoscopy was attempted on two occasions but could not be done because of mechanical difficulties. The patient has been treated with streptomycin and calciferol separately, but not concurrently.

DISCUSSION

DR. H. E. MICHELSON, Minneapolis: I think that, since lupus vulgaris is a rare disease, when we see such a wonderful example it is bound to provoke some remarks. The patient is American-born but of Polish extraction. She is 49 years old and has had the condition for 25 years. She shows several characteristic changes of long-standing lupus vulgaris. When lupus vulgaris is allowed to go without treatment, or even if ineffective treatment has been used, the end result is going to be atrophy with either scarring or ulceration, occasionally verrucous formations, and, as you know, degeneration with cancer. In her case the plaque is largely atrophic, but in two areas the lesions are moist and elevated, and I think an excision should be made with cancer in mind. As far as the connection with systemic tuberculosis is concerned, her husband died of pneumonia, and her chest roentgenograms are said to show signs which may be tuberculosis. The usual statistics quote 30% of lupus vulgaris patients with pulmonary tuberculosis, but I think the percentage is much too small, for we know that there are many types of tuberculosis of the lung that cannot be demonstrated with certainty. Up to the time when chemical therapy was instituted, patients of this type did not attain very good results, and, even now, in long-standing cases there may be response to a certain degree to vitamin D and then a standstill. I think she would be a suitable patient on whom to try various combinations, and paraaminosalicylic acid might well be tried.

DR. ADOLPH ROSTENBERG: My chief reason for talking is to draw your attention to an excellent article on the treatment of skin tuberculosis with calciferol (*Dermatologica* **101**:1, 1950). The article is based on a study of 350 cases. Many of the points Dr. Michelson brought out are emphasized. The authors used 50,000 units of calciferol three times a day. If they treated patients for only six to nine months, they had three times as many relapses as when they continued the treatment for a year or more.

In connection with one of Dr. Michelson's remarks on the incidence of pulmonary involvement, the Scandinavian authorities who see a lot of lupus vulgaris say the cutaneous reactivity is less when there is a concomitant pulmonary involvement. When one is suspicious of this, a tuberculin test might be of some value.

DR. STEPHEN ROTHMAN: This patient has a papular follicular eruption which, clinically, might very well be lichen scrofulosorum. We presented here a patient with extensive lichen scrofulosorum after treatment of the lupus with vitamin D_2 (ARCH. DERMAT. & SYPH. **57**:392, 1948). Sudden involution of lupus tissue as it occurs during vitamin-D_2 therapy might promote the development of tuberculids.

Among the old treatment methods, localized and generalized ultraviolet ray irradiations were highly effective without being caustic.

In the large material of lupus patients I saw in Germany, active tuberculosis of the lungs was extremely rare. Most of them had nonactive fibrous pulmonary processes. They died from miliary tuberculosis or from tuberculous meningitis but not from tuberculosis of the lungs.

Herpes Gestationis. Presented by DR. DAVID OMENS (by invitation), DR. HAROLD OMENS, and (by invitation) DR. STEFAN BIELINSKI.

DISCUSSION

DR. LEON GOLDMAN, Cincinnati (by invitation): The excuse for discussing this case is to talk about treatment with topical cortisone. We are aware of the local use of cortisone ("cortone") in pemphigus and in psoriasis. Our experiences with cortisone by topical application, by intradermal injections, and by the hypospray® jet-injection apparatus so far have not been too successful. Injections may cause nodules, and detailed histochemical studies have been made of the reactions to cortisone crystals and to the vehicle in tissue. We have used 150 mg. per ounce of vehicle for ointments. It has been suggested that we use even higher concentrations, and with the help of Merck & Company, Inc., we plan to do this.

DR. M. J. REUTER, Milwaukee: Dr. Goldman mentioned cortisone. I have had a patient under my care periodically for the past 10 years because of a severe type of bullous herpes gestationis which occurred during each of three previous pregnancies and at no other time. At

the present time she is again pregnant and has a severe type of dermatitis herpetiformis or herpes gestationis. In the first two pregnancies we were able to control the eruption with sulfapyridine. During the last pregnancy three years ago the eruption was not controlled, and the patient spent six months of her pregnancy in the hospital. She is now five-months pregnant, and the herpes gestationis appeared at two and one-half months. We tried treatment with sulfapyridine again and various other medicaments without success. Rather desperate, we started cortisone therapy, 150 mg. for a first dose, then 100 mg. daily for five days. She had, after a week, a very gratifying result with complete disappearance of the eruption. She is now taking cortisone by mouth in 100-mg. doses every three to four days. With this dosage, the disease has been kept under control, and she is quite comfortable. I tried to find out the effect of corticotropin and cortisone on pregnancy, especially in regard to danger to the fetus, but I have had no success.

DR. HAROLD SHELLOW: There are some features of this eruption which are suggestive of a fixed exanthem, dermatitis medicamentosa, especially the development of what appear to be isolated bullae surrounded by pigmentation. The patient's history was not clear, though she states that she had some sort of an eruption in between her pregnancies. She readily admitted that for some six or seven years she had been taking phenolphthalein in the form of ex-lax® regularly twice a week. It is difficult to rule out herpes gestationis, but the thought again comes to my mind whether the use of phenolphthalein during pregnancy might enhance this action.

DR. C. W. FINNERUD: Dr. Szymanski and I intended to show a patient today with the most severe dermatitis herpetiformis we have ever seen. He was seen again yesterday and for the first time was so much better that it was not worth while showing him. He has been to several physicians and has taken everything known to be of value without benefit. He decreased in weight markedly and was extremely nervous. We started treatment with sulfoxone sodium (daisone®) a while ago, as suggested by Dr. Cornbleet, having his blood checked periodically; and he showed marked improvement rapidly. His blood picture has remained normal, and he now sleeps well and has gained back most of his lost weight. Dr. Szymanski might elaborate on the treatment he has had in the past.

DR. F. J. SZYMANSKI: As Dr. Finnerud has told you, we have been using sulfoxone sodium in the treatment of dermatitis herpetiformis. The dosage consists of 0.15 gm. three times daily. At the present time we have four patients with dermatitis herpetiformis who are resistant to sulfapyridine, but sulfoxone sodium has controlled their itching and has prevented recurrences. This drug is not completely innocuous inasmuch as it does have a toxic effect on the bone marrow in some cases. Therefore, we have advised weekly blood counts on our four patients. Erythema nodosum is the only other toxic complication that has been reported.

DR. ADOLPH ROSTENBERG: There is a recent article in the *Medical Journal of Australia* (Dec. 2, 1950) on the use of folic acid in conjunction with sulfapyridine. As the author points out, this has a therapeutic rationale, for sulfapyridine used experimentally can create a folic acid deficiency which in turn may conduce towards a neutropenia. Consequently, he suggests using folic acid 10 to 20 mg. per day in conjunction with sulfapyridine.

In answer to Dr. Reuter about the use of cortisone during pregnancy, we had as a patient a pregnant woman with a chronic atopic dermatitis, and this problem came up. We consulted the Armour Laboratories, and it was their opinion that if the dose were small enough there was no risk to mother or fetus in continuing either cortisone or corticotropin through pregnancy.

A Case for Diagnosis. Presented by DR. DAVID OMENS (by invitation), DR. HAROLD OMENS, and (by invitation) DR. J. F. SICKLEY.

The patient is a 41-year-old Negro man. About four months ago he noticed a small "pimple" on his left cheek. This itched slightly, but he paid no attention to it. In the past four months the area involved has become progressively larger and depigmented. There have been no other complaints, and there is no history of syphilis.

On the left side of the face there is a circumscribed lesion. In the center of the lesion there is a partial alopecia and patchy areas of depigmentation. The border of the lesion is slightly

erythematous and crusted. There is also slight elevation of the border of the lesion. In the bearded region of the neck there is a mild papular dermatitis. There is no cervical adenopathy.

Laboratory findings were as follows: hemoglobin 75%; white blood count 3,700; polymorphonuclear leucocytes 49%, lymphocytes 37%, monocytes 14%. Results of urinalysis and a roentgenogram of the chest were normal. Serologic reactions for syphilis were negative. No fungi were found in scrapings from the lesions. A culture (Sabouraud) showed no growth at the end of two weeks. Biopsy of the skin revealed a nonspecific inflammation.

DISCUSSION

DR. FRANCIS W. LYNCH: I think this eruption was one of the most interesting presented today. Syphilis seems to be excluded, leaving three disorders to be considered in differential diagnosis: lupus vulgaris, blastomycosis, and lupus erythematosus. For the first, there is not much evidence. This plaque with continuous marginal involvement did not have the irregularity of outline or those changes in the central portion that one would expect with lupus vulgaris, nor did the sections support that diagnosis. Seldom do lesions of blastomycosis become as large as this without becoming thicker, and, again, the microscopic evidence did not support that diagnosis. Finally, I would favor lupus erythematosus. The sections showed a good deal of hyperkeratosis in some large follicular areas, and there appeared to be changes in the connective tissues, supporting diagnosis of the hyperkeratotic form of lupus erythematosus.

DR. S. W. BECKER: It was a most remarkable picture. He said he first had a tiny lesion, and he put something on it, and then it spread. I think it is probably factitial.

DR. CARL W. LAYMON, Minneapolis: I agree with Dr. Lynch, but also thought of the possibility of a lupoid sycosis. Granting that there is no pathognomonic histologic picture for lupus erythematosus, I thought that these sections were against such a diagnosis, though clinically it was a definite possibility.

DR. M. R. CARO: I think there is ample evidence both clinically and histologically against all the diagnoses that have been offered except the one suggested by Dr. Becker. In lupus erythematosus in as active a stage as this I would not expect to find any eosinophiles in the infiltrate, but there were quite a few present. Against the diagnosis of lupoid sycosis, none of these areas clinically or microscopically showed any follicular infection. I think that this is a case of a dermatitis of nonspecific nature, probably self-induced.

Sclerosing Hemangioma. Presented by DR. J. GINSBERG and (by invitation) DR. D. MUSGRAVE.

P. G., a 68-year-old white man from the Dermatology Clinic of Northwestern University Medical School, has had a purplish soft nodule over the lateral aspect of the right ankle for 40 years. The lesion measures about 0.5 by 1.5 cm., and there is a 2-by-3-mm. elevation. The patient is quite sure that the lesion was not present at birth. He is not sure whether the lesion followed trauma to the feet.

Report of microscopic examination follows. A hematoxylin-and-eosin-stained section revealed typical intracutaneous masses of capillary tumors, with hyalinization of collagen between and about the vessels. Brown pigment granules (hemosiderin) were distributed in and about the capillary masses, with increase in the number of thick-walled larger blood vessels. There was pressure atrophy and hyperkeratosis of the epidermis.

A potassium-ferrocyanide-stained section showed the regular-sized blue granules of hemosiderin, intracellularly and extracellularly, deposited both in and about the blood vessel masses.

Orcein-Weigert elastic tissue stain showed absence of elastic fibers in the capillary tumor masses.

DISCUSSION

DR. HAMILTON MONTGOMERY, Rochester, Minn.: This case brings up a question of terminology. Strictly speaking, the term used above accurately describes the lesion in this case because the histopathologic changes are those of a sclerosing hemangioma, or better, hemangioma or angioma with sclerosis. Gross and Wollbach introduced the term "sclerosing hemangioma"

for a different condition which had variously been termed in the past nodular subepidermal fibrosis and dermatofibroma, histiocytoma, and multiple variations of these terms. Senear and Caro preferred the term, "histiocytoma," because in the majority of their patients there were deposits of lipids and especially deposits of hemosiderin. Wollbach and Gross in their series had lesions appearing on the face in children with an antecedent history of angioma going back to childhood. A former fellow of mine, Dr. Rentiers, and I reviewed a large series of cases of patients with these discrete nodular lesions in the skin and believe that all can be grouped under the term "nodular subepidermal fibrosis," with variants being classified, if one wishes, as dermatofibroma, histiocytoma, and sclerosing hemangioma, respectively, dependent on the predominance of the various histopathologic changes. In our series of patients there was no antecedent history of hemangioma. The majority of the lesions failed to show increase in deposition of hemosiderin or lipids.

I do not believe that the case presented by Drs. Ginsberg and Musgrave belongs in the group of nodular subepidermal fibrosis but represents a true angioma that has undergone fibrosis.

Dr. Hermann Pinkus, Monroe, Mich.: As Dr. Montgomery pointed out, what the general pathologists diagnose as sclerosing hemangioma, we dermatologists call dermatofibroma, histiocytoma, or just nodulus cutaneus. The speed with which the term sclerosing hemangioma has been accepted by pathologists throughout the country has been very surprising to me. I think the evidence for this concept is far from complete and entirely disregards all the work published in the dermatologic literature. I am pleased to note that recently a few dissenting voices have been heard, even among the general pathologists. The case presented here today is of different nature. I agree with Dr. Montgomery that it is a hemangioma which shows evidence of sclerosis, and in this sense, the term sclerosing hemangioma is properly applied to it. It may be wise, as Dr. Montgomery says, not to use this term in this connection, however, in order to avoid more confusion.

Dr. Julius E. Ginsberg: I showed this patient because of the confusion in the terminology of these lesions. I did think it was worth while to introduce the viewpoint of a man from another part of the country in regard to origin of these small benign lesions.

The differential diagnosis included Kaposi's sarcoma and ancient granuloma pyogenicum. The history and microscopic findings, and particularly the physical findings, are those of the entity described by Wollbach and Gross in their article in the *Journal of Pathology*, July, 1943.

Foreign Body Granuloma, Sarcoid-Like. Presented by Dr. M. C. Spencer, Danville, Ill. (by invitation).

C. B. is a 36-year-old white man of English extraction. His family history is not significant, and past medical history is noncontributory. Approximately 15 to 18 years ago, the patient suffered a laceration of the left little finger on a meat grinder. This injury healed uneventfully, although complete healing did not occur for about three or four weeks after the injury. The patient reports that during the entire time of healing the finger was bandaged.

The patient was first seen by me on Oct. 10, 1950. At that time, he reported that the present lesion had been developing for the last six weeks. He denied that it had been preceded by any trauma. He denied having been injured in the past by any broken fluorescent bulbs, nor had he worked around or with beryllium. He did, however, state that approximately four or five years ago, he worked in an aluminum plant where he often cut aluminum metal.

Although he reported that since the time of development the lesion had gradually increased in size, there has been little change in the size of the lesion since his initial examination in October. Actually, following biopsy on Oct. 11, there seemed to be some clinical regression in the size of the lesion.

General medical examination reveals a well-nourished, normally developed white man of stated age, and no apparent distress. The general physical examination gave essentially normal results.

Dermatologic examination reveals on the extensor surface of the left fifth finger, overlying the interphalangeal joint, a dusky erythematous tumor measuring approximately 2 by 1 cm. in its

greatest diameter and elevated above the skin surface by about 0.5 cm. On palpation it is slightly tender and has a hard and nodular feeling of a fibrous lesion. It is freely movable and is not fixed to underlying structures.

A surgical section was taken for biopsy from the central portion of the lesion Oct. 11, 1950.

Microscopic examination showed hyperkeratosis, acanthosis, nests of epithelioid cells in the dermis, some Langhans' giant cells, and lymphocytes. There are numerous doubly refractile crystals in the granulomatous tissue (not inside the giant cells) which do not look much like particles of sand as seen under polarized light, but which may be. The crystals are strikingly demonstrated with polarized light.

The diagnosis was granuloma, type undetermined (silicon?).

A roentgenogram of the chest on Nov. 21, 1950, showed increased trunk markings in the left apex, with several small areas of fibrous density. There was no evidence of any active pulmonary pathologic process, and the heart appeared within normal limits. A roentgenogram of the chest on Dec. 24, 1950, showed the condition to be essentially unchanged.

Serologic test on Nov. 22, 1950, elicited a negative reaction.

This case has not been presented before. The presented diagnosis is foreign-body granuloma, sarcoid-like.

DISCUSSION

DR. HERMANN PINKUS, Monroe, Mich.: My first clinical impression was that of granuloma annulare, but the color was not quite right. The histologic section left no doubt about this being a foreign-body granuloma, with the beautiful demonstration of many crystals under the polarizing microscope. I would not be surprised if the old injury had a connection with the development of this lesion. The crystals may be silicon or talc, which also is a silicate. Such granulomas may develop many years after the implantation of the foreign material. In one case a sarcoid-like talc granuloma which I had occasion to diagnose developed in the conjunctiva 14 years after operation for strabismus (McCormick, G. L.; Macauley, W. L., and Miller, G. E.: Talc Granulomas of the Eye, *Am. J. Ophth.* **32**:1252 [Sept.] 1949). Since the differential diagnosis of granulomatous lesions has become more complicated by the appearance of beryllium granulomas, I have made it a practice to examine all granulomatous lesions around the face under the polarizing microscope and also with filtered ultraviolet rays. I have picked up a few foreign-body granulomas that way which might have passed as sarcoid lesions otherwise. One must be cautious, however, in interpreting double-refractile matter in giant cells. Small particles of horny matter from degenerating hairs also show up under the polarizing microscope.

DR. M. C. SPENCER, Danville, Ill. (by invitation): During the last two weeks, this lesion has obviously regressed in size. Furthermore, subjective symptoms have decreased. It is of interest that the patient originally consulted me because of pain associated with the lesion. Since the reduction in size, pain has also decreased. One point in the history which may be of real significance is the fact that the patient tells of roofing a building two years ago with shingles made of fireproof material coated with sand. He reports that he did not wear gloves while doing this work. It seems likely to me that the source of silicon was during this procedure.

Lichen Sclerosus et Atrophicus. Presented by DR. STEPHEN ROTHMAN and (by invitation) DR. E. FARNEY-DAVIES.

M. S., a 5-year-old white girl, first seen at the University of Chicago Clinics Dec. 28, 1950, was well until three years ago, when she began to experience itching of the vulva and perineum. Skin changes, notably a change from natural to gray color, were observed first by the mother, one year after onset of pruritus. The disease process spread gradually to the perianal area and caused painful fissuring of the anus. During the past year, no further extension has occurred. Pruritus and discomfort during defecation have been the main complaints. Soothing sitz baths, application of a bland ointment locally, and measures to keep stools soft have resulted in great improvement.

Findings from physical examination are noncontributory except for skin changes. The vulva, perineum, and perianal areas display a waxy white color surrounded by reddish-brown flare.

The white areas are smooth, slightly wrinkled, and nonindurated. Around the anterior commissure some fine depressed elements of the surface are visible.

Laboratory studies revealed the blood count and urine to be within normal limits. A roentgenogram of the chest was normal. One examination showed the stool negative for parasites and ova.

Biopsy of a section showed slight hyperkeratosis, atrophic epidermis, hemogenization and edema of the connective tissue in the upper corium, and a band of lymphocytic infiltrate below the homogenized area. Elastic stain showed complete absence of elastic fibers in the upper corium.

Lichen Sclerosus et Atrophicus. Presented by DR. M. H. EBERT and (by invitation) DR. B. YAFFE.

M. A., a 65-year-old white woman, has been attending the Gynecology Clinic of the Central Free Dispensary since 1943 with the complaint of vulvar pruritus. Diagnoses had ranged from atrophic senile vaginitis, kraurosis vulvae, to leucoplakic vaginitis.

Treatments included local applications of methylrosaniline chloride, potassium permanganate douches, diethylstilbestrol-U. S. P. suppositories, dibucaine hydrochloride-N. F. (nupercaine®) ointment, and surgical vulvectomy. She was referred to the dermatology clinic in December, 1950.

Examination showed the vulvar skin area to be atrophic, labial folds absent, and introitus constricted. In addition there were scattered atrophic patches over the thighs, lower abdomen, inframammary area, and lumbar region. These patches were irregular in outline, ivory-colored, with tissue-paper atrophy and fine scaling. At the borders polygonal outlined macules were present which coalesced to form the main atrophic patches.

Biopsies were done on specimens taken from the genitalia and trunk; and local therapy was outlined.

Symptomatic improvement has occurred with relief of the pruritus.

Laboratory tests were noncontributory.

DISCUSSION OF TWO PRECEDING CASES

DR. CARL W. LAYMON, Minneapolis: When lichen sclerosus appears in childhood, at least in females, it is most commonly localized to the genitals, although occasionally lesions appear elsewhere on the body. In older persons, both males and females, the reverse is true. It is my opinion that kraurosis vulvae and kraurosis penis are forms of lichen sclerosus. I think that the obliterative changes in the blood vessels are of less importance than we formerly believed. Lichen sclerosus, both in males and females, can be complicated by leucoplakia.

DR. HAMILTON MONTGOMERY, Rochester, Minn.: This young child is of great interest because of the young age of onset of the lichen atrophicus of the vulva without evidence of leucoplakia or of kraurosis. Histologically there are definite changes in the blood vessels, which as a rule do not occur in lichen sclerosus et atrophicus, in contrast to thickened vessels as seen in kraurosis. Biopsy of sections from this child showed hyalinization of the vessel walls, such as one sees in acrosclerosus or other forms of scleroderma. Some of the vessels, especially near the sweat glands, revealed almost complete obliteration of their lumens. This is most remarkable, especially if one considers the age of the individual. Confusion occurs between lichen sclerosus kraurosis and leucoplakia of the vulva arising in women at the time of the menopause if one or more of these conditions is occurring simultaneously.

In the case presented by Dr. Ebert and Dr. Yaffe, the patient also had typical lichen sclerosus and atrophicus beneath the breasts. I have seen lichen sclerosus in both children and adults involute, but I have not seen kraurosis vulvae involute. It is unfortunate that lichen sclerosus of the vulva, which always has a characteristic ring-shaped perianal involvement, which in itself distinguishes it from leucoplakia of the vulva, should be confused with leukoplakic vulvitis. Lichen sclerosus, unlike leucoplakia, is not a precancerous lesion, and vulvectomy is not indicated.

DR. A. B. FALK: I should like to make further report on the case we showed at the November meeting from the Children's Memorial Hospital. Although the patient had had a pinworm infestation in the past, an examination at the time of presentation revealed a stool to be negative

for pinworm. The girl continued to be well for some time after the meeting, then she suddenly began to itch, and on examination we discovered pinworms again. I suspect that the association of pinworms and lichen sclerosus et atrophicus in young girls is more than coincidental.

DR. ADOLPH ROSTENBERG: We have seen several of these cases in children. Has anyone followed them for a reasonable period of time? What is the ultimate prognosis?

DR. S. W. BECKER: I cannot answer Dr. Rostenberg's question, but there are interesting facts about kraurosis vulvae. I have seen gynecologists make a diagnosis of kraurosis vulvae in patients who had only pruritic dermatoses of various sorts about the vulvae, neurodermatitis, etc. I had occasion to go over many sections with a Chicago gynecologist who was studying the subject of kraurosis vulvae, and at least 50% of the sections were typical for lichen sclerosus et atrophicus. I cannot believe that lichen sclerosus et atrophicus is the same as kraurosis vulvae. I think there is a distinction which can be made clinically and microscopically.

DR. CARL W. LAYMON, Minneapolis: I think that the process is reversible at all ages. I have seen adults in whom the disease disappeared without leaving a trace. We have also seen cases in children in which there was complete involution at the time of puberty.

DR. FREDERICK BECKER, Duluth, Minn.: Dr. Laymon, I am sure, answered Dr. Rostenberg's questions. During the last 14 years I have had three children with this condition under close observation. At the onset of menses and puberty, the condition spontaneously underwent remission. I have been observing one patient with lichen sclerosus for the past 10 years whose case was presented and diagnosis confirmed by the Minnesota Dermatologic Society five years ago. Recently indurated leucoplakic areas developed, which on biopsy showed a grade 1 cancerous condition. She has had a simple vulvectomy for control of the cancer. Therefore, I think there is a very close relationship between lichen sclerosus and kraurosis vulvae and leucoplakic vulvitis.

DR. M. H. EBERT: The combination of lichen sclerosus et atrophicus and leucoplakia on the vulva is not uncommon, according to Nomland. It is a striking fact that lichen sclerosus et atrophicus is seen at the extremes of life. We see it in children and in women that have passed the menopause. I presume it is the influence of the sex hormones that causes the lesions to undergo involution as soon as the child matures, and later after the menopause the lesions reappear.

A Case of Tinea Capitis (Audouini) with Tinea Ciliorum in a Boy of Eight. Presented by DR. JAMES HERBERT MITCHELL and (by invitation) DR. ROBERT M. GOODWIN, Springfield.

T. H., a boy aged 8 years, was seen in the office of one of us (R. M. G.) for typical dry patch ringworm of the scalp, of six weeks' known duration. The history and findings were in no way extraordinary.

Definite fluorescence of five of the cilia of the right upper lid was seen. Two of these cilia were washed in ether after forceps epilation, and still fluoresced. The remaining three were sent unwashed to Dr. Mitchell for culture, along with a specimen of affected scalp hairs. Microsporum audouini was recovered from each specimen.

Dr. Mitchell's report follows. Three cilia were submitted for examination. All three fluoresced typically for M. audouini. Each of the three cilia was placed on a separate Sabouraud agar slant. Each hair produced a typical colony of M. audouini.

The three tubes and a microscopic preparation are submitted, together with a report of a case by Royal M. Montgomery and Esther A. Walzer (ARCH. DERMAT. & SYPH. **46**:40-43 [July] 1942).

Paget's Disease of the Nipple. Presented by DR. THEODORE CORNBLEET, DR. DAVID COHEN, and (by invitation) DR. J. F. SICKLEY.

Pyoderma Gangrenosum. Presented by DR. HERBERT RATTNER, DR. HAROLD RODIN, and (by invitation) DR. STEFAN BIELINSKI.

A Case for Diagnosis: Nodular Eruption. Presented by DR. THEODORE CORNBLEET, DR. DAVID COHEN, and (by invitation) DR. J. F. SICKLEY.

Hereditary Keratoderma Palmaris et Plantaris. Presented by DR. MICHAEL EBERT, DR. VERA LEAF, and (by invitation) DR. J. F. SICKLEY.

Psoriasis of the Mucous Membrane? Leucoplakia? Presented by Dr. James Webster, Dr. Samuel Bluefarb, and (by invitation) Dr. J. F. Sickley.

Subacute Disseminated Lupus Erythematosus. Presented by Dr. James Webster, Dr. Samuel Bluefarb, and (by invitation) Dr. Stefan Bielinski.

Subacute Disseminated Lupus Erythematosus. Presented by Dr. Ashton L. Welsh, Cincinnati.

Case for Diagnosis (Von Recklinghausen's Disease? Early Scleroderma?). Presented by Dr. Ben C. Schwartz (by invitation), Dr. E. J. Rossman (by invitation), and Dr. Cleveland J. White (by invitation).

Pityriasis Lichenoides et Varioliformis Acuta. Presented by Dr. Francis E. Senear and (by invitation) Dr. Louis Rubin.

Case for Diagnosis (Leukemid). Presented by Dr. Theodore Cornbleet.

Multiple Mitotic Growths and Keratoses (Arsenical?). Presented by Dr. Stephen Rothman and (by invitation) Dr. Richard B. Stoughton.

Keratosis Follicularis (Darier's Disease). Presented by Dr. David Cohen and Dr. Theodore Cornbleet.

Pityriasis Rubra Pilaris. Presented by Dr. Stephen Rothman and (by invitation) Dr. Lydia C. Marshak.

Erythroderma Exfoliativa (Secondary to Pityriasis Rubra Pilaris?). Presented by Dr. Stephen Rothman and (by invitation) Dr. Lydia C. Marshak.

Lichen Planus. Presented by Dr. F. E. Senear and (by invitation) Dr. J. M. Riddell.

Stephen Rothman, M.D., *President*

James R. Webster, M.D., *Secretary*

Feb. 21, 1951

Koilonychia. Presented by Dr. Herbert Rattner, Dr. Harold Rodin, and (by invitation) Dr. J. F. Sickley.

DISCUSSION

Dr. Harold H. Rodin, South Bend, Ind.: The principal reason for presenting this patient was her familial history. She stated that two aunts and one daughter had the condition. Another interesting feature of the case was the lack of underlying diseases which are usually associated with this condition. The patient did not have a secondary anemia, and she did not show any evidence of avitaminosis.

Metastatic Melanoblastoma. Presented by Dr. David Omens, (by invitation) Dr. Harold Omens, and (by invitation) Dr. Stefan Bielinski.

The patient is a 39-year-old woman. About six months ago a firm nodule developed in the left pectoral region. About two months later another nodule developed just above the left clavicle. Since that time she has noticed similar firm subcutaneous nodules on the left mandible, left upper arm, and left breast. The lesions are tender for a few days, but following this they are asymptomatic. The patient states that all the nodules are getting progressively larger.

The patient has not felt sick and has not lost any weight.

Two years ago her right eye was removed because of a cancerous melanoma.

The patient presents several bluish, firm nodules in the left anterior shoulder region. They are fixed to the skin but not to the underlying tissue. Subcutaneous nodules are palpable over the left mandible, left upper arm in the deltoid area, and the left breast.

Laboratory findings were as follows: Results of urinalysis were normal. Hemoglobin was 63%; red cells, 4,680,000; white cells, 8,300; total protein, 7.2 mg.; nonprotein nitrogen, 34 mg. Serologic reactions were positive.

A chest roentgenogram showed a density in the left first interspace.

A skin biopsy revealed a cancerous melanoblastoma.

DISCUSSION

Dr. Stephen Rothman: A verbal report from Knoxville, Tenn., intimated that radioactive iodine is being accumulated in cancerous melanomas, and that patients treated with radioactive iodine have shown involution of tumors. Unfortunately, in one of our patients with widespread metastases this observation could not be confirmed by Dr. Dwight Clark in our surgery department. There was no selective uptake of radioactivity whatsoever. Similarly, Dr. Lorincz in our laboratory could not find any accumulation of radioactive iodine in the Cloudman strain of transplantable cancerous mouse melanomas.

Acrosclerosis Being Treated with Corticotropin (ACTH). Presented by Dr. E. A. Oliver and staff.

Linear Scleroderma Treated with Corticotropin (ACTH). Presented by Dr. E. A. Oliver and staff.

DISCUSSION OF TWO PRECEDING CASES

Dr. Theodore Cornbleet: It seems that the effect of corticotropin (ACTH) on scleroderma depends on the stage of the disease. The one patient to whom I administered a fair trial with it was past the early edematous stage and in the middle one. He did not improve, and I would not expect the disease in its later stages of atrophy to respond, either. There are changes present in the x-ray diffraction pattern after the use of corticotropin, even though the clinical improvement is minimal. This may mean that scleroderma is not necessarily irreversible.

Dr. Adolph Rostenberg: One of the important things to realize about scleroderma is that it is a systemic disease. Possibly we should not speak of scleroderma but rather of systemic sclerosis. Dr. Rothman has written on that. Recently there was an excellent article by Beerman (*Am. J. M. Sc.* **216**:458 [Oct.] 1948) discussing the systemic manifestations.

Dr. F. J. Szymanski: I had an opportunity to study a case of generalized scleroderma at autopsy. To my amazement, the striated muscles showed histopathologic changes quite similar to those of dermatomyositis. The basement membrane of the glomeruli was thickened and sclerotic and very much like the "wire-loop" kidney of disseminated lupus erythematosus. The skin, esophagus, blood vessels, and connective tissue revealed the typical changes of scleroderma. From a morphologic viewpoint, one can readily believe that a close relationship exists amongst these various collagen diseases.

Dr. J. M. Riddell, Jr. (by invitation): The postmortem findings in our patient who had generalized scleroderma were reviewed briefly by Dr. Szymanski. Another patient with far advanced generalized scleroderma was treated by the medical service at the Research and Educational Hospital with large amounts of corticotropin and also some cortisone. I believe that these drugs in no way prevented the death of these patients. Kidney complications developed and they died in uremia. It will be a while before we know what corticotropin does in scleroderma. I shall be very interested to learn how the patient whose condition was diagnosed as acrosclerosis responds to his treatment. He had been under our observation for one year. His disease process is already far advanced, and I question the value of giving corticotropin to this man.

Dr. F. R. Schmidt: I am somewhat hesitant about reporting results with a new type of treatment for scleroderma. My experience is limited to five patients, the treatment consisting of infusions of a 0.1% solution of procaine hydrochloride. The improvement in the color, texture, and elasticity of the skin and mucous membranes has been truly remarkable. All the patients have noted an improvement in chewing and swallowing their food after one week, and some after three or four days. There was more flexibility in the finger joints, and the skin became softer. The results were published in *The Journal of the American Medical Association* (**144**:1550 [Dec. 30] 1950). We should like to get some patients with this disease in its very early stages in whom this treatment could be tried.

Dr. Calvin J. Dillaha (by invitation): At the University of Chicago Clinics we treated one patient with diffuse scleroderma with corticotropin. During the course of the therapy symptomatic relief occurred, lasting only as long as therapy was continued. The patient's appetite improved, and she felt much better. Objectively, however, no significant change could be noted, and we felt that the progression of the disease was not influenced by corticotropin.

Dr. Stephen Rothman: The patient with linear scleroderma is particularly interesting because of the radicular or neuritic pain which accompanied the development of the lesion. This combination again seems to indicate that linear scleroderma may be a trophoneurotic disease (Rubin L.: Linear Scleroderma, Arch. Dermat. & Syph. **58**:1-18 [July] 1948).

Concerning the systemic nature of diffuse scleroderma, the involvement of the heart was not mentioned in this discussion. Several cases have been reported in which patients had severe changes in the connective tissue septa of the heart muscle. We lost a young woman with sclero-

derma who had no atherosclerosis and no syphilis. She complained of substernal pain which was not due to esophageal involvement, and died suddenly from an "anginal heart attack."

DR. H. H. RODIN, South Bend, Ind.: I would like to ask Dr. Schmidt if he thinks his result with procaine is based on the action of paraaminobenzoic acid on the collagen system or on the neurovascular mechanism of the involved blood vessels.

DR. F. R. SCHMIDT: I have asked some chemists about this, and they believe that the action is due to paraaminobenzoic acid.

Our work is based on the work of Graubard and Peterson in arthritis. I believe that there is hypertonia of the sympathetic nervous system which is then affected by procaine.

Sarcoidosis. Presented by DR. JAMES WEBSTER, DR. SAMUEL BLUEFARB, and (by invitation) DR. J. F. SICKLEY.

The patient is a 39-year-old Negro man who entered Cook County Hospital on Feb. 2, 1951, complaining of cough, dyspnea, and weakness of two weeks' duration. Since 1940 he has had frequent colds and states that in 1941 a cold developed which was followed by a "pimple" on his face. Since this time he has had frequent recurrences of "pimples" on the upper lip, and in 1948 he began having similar lesions about the mouth and nose. In the past three months the eyelids have become inflamed.

In the past four weeks he has lost about 5 pounds (2.3 kg.) of weight, and three days prior to entry into the hospital hoarseness developed. There is no history of hemoptysis, chills, fever, or night sweats.

The patient presents violaceous, granulomatous lesions of the chin, upper lip, nose, and the eyebrow region. The skin of the nose is telangiectatic, and the right ala nasae is retracted.

There is bilateral enlargement of the epitrochlear lymph nodes, and there are numerous small, shotty, discrete, firm, nontender nodes in the cervical, axillary, and inguinal regions.

Results of urinalysis were normal. Laboratory studies of the blood revealed the following findings: hemoglobin, 97%; red cells, 5,150,000; white cells, 5,000; neutrophils, 75%; eosinophils, 2%; band-form polymorphonuclear leucocytes, 3%; lymphocytes, 15%, and monocytes, 5%. Serologic reactions for syphilis were negative. Total protein was 8.6 gm. (4.0 gm. of albumin and 4.6 gm. of globulin); calcium, 10.7 gm.; phosphorus, 4.3 gm.; alkaline phosphatase, 1.5 units; acid phosphatase, 0.1 units. Reaction to the Mantoux test (1:1000) was negative. Report on a chest roentgenogram was as follows: "There is a nonhomogenous increase in density of both apices with a calcified nodule on the right." Biopsy of a specimen of an epitrochlear node revealed Boeck's sarcoid. The report on a skin biopsy specimen stated that it revealed sarcoid.

DISCUSSION

DR. ADOLPH ROSTENBERG: In this case the condition conformed to the usual diagnostic criteria of sarcoidosis, both morphologically and pathologically. As I recall, both the skin and the lymph nodes showed sarcoid lesions. Roentgenologically there were some changes in the lung. Dr. Ebert thought he noticed changes in some of the phalanges. Immunologically the patient failed to react to tuberculin at 1:1000.

The big problem is, what is sarcoidosis? There have been many speculations as to the nature of the disease. Probably the most commonly held theory is that it is some form of tuberculosis and that the patient has an altered response to the tubercle bacillus in the form of enhanced resistance. There is not time to go into the arguments pro and con, but I do not believe such a view has any basis in fact or in theory.

I think we are at the threshold of our knowledge of sarcoid. In many places numerous workers are doing studies of various nature on sarcoidosis. For example, a very interesting study was reported by Michael and his group at Emory University (*Am. Rev. Tuberc.* **62**:403-407, 1950). They studied a large number of cases of sarcoidosis. They found a significant difference in the distribution of sarcoidosis, persons from the southeastern part of the country being disproportionately afflicted. They also found that many persons with sarcoidosis have been born and reared in rural communities. What is the significance of these findings? Certainly it is not consistent with the belief that the disease is tuberculosis.

Dr. Senear, Dr. Szymanski, Dr. Haeberlin, and I are doing studies on animals. We are inoculating animals which have sarcoidosis with BCG, and at varying times later extirpating

a bit of the inoculated area and staining it for tubercle bacilli. So far, in two instances the organism was found in large numbers on the fifth day. In one case the organisms were still there on the 10th day. We think it self-evident that the finding does not indicate an ability to dispose of the tubercle bacillus in any enhanced fashion.

DR. F. J. SZYMANSKI: Injection of BCG into the skin of patients with sarcoidosis produced a lymphocytic cell infiltrate on the fifth day after the injection. One the 12th day following injection of BCG, histologic section from the injected site revealed an inflammatory response which consisted predominately of large histiocytes with only an occasional lymphocyte. However, the picture did not resemble the masses of epithelioid cells characteristic of sarcoidosis.

DR. STEPHEN ROTHMAN: The high total plasma protein and high globulin values in this case are rather characteristic of sarcoidosis.

Fox-Fordyce Disease (in a Male). Presented by DR. S. J. ZAKON and (by invitation) DR. A. L. GOLDBERG.

B. K., a white youth aged 19, was first seen in December, 1950. He complained of itching of the armpits and noticed the appearance of papules. This condition had then been present for about four months. The symptoms persisted in spite of treatment.

Physical examination reveals a well-developed, well-nourished, white youth. Discrete, sharply circumscribed papules are present in the axillae. The hairs are absent in many areas. Occasionally inflammatory swellings have been noticed in the armpits.

He received x-ray therapy and local therapy without any apparent benefit. A biopsy was done, and a diagnosis of chronic dermatitis was made. Male sex hormones were administered with some improvement.

Fox-Fordyce Disease. Presented by DR. S. J. ZAKON and (by invitation) DR. A. L. GOLDBERG.

DISCUSSION OF CASES OF FOX-FORDYCE DISEASE

DR. THEODORE CORNBLEET: When Dr. Zakon told me he had a male patient with Fox-Fordyce disease, I looked forward to seeing my first such case. I feel, however, that I cannot agree to that diagnosis here, even though the sites of the lesions suggest it. The central parts of the eruption at each location are solid patches, with lichenoid components peripherally only. This to me is the appearance of lichen simplex chronicus. In addition, the hair growth in the axillae remains intact, which is not regularly seen in Fox-Fordyce disease. Naturally, in such an unusual situation as this, one would want histologic corroboration, and that is entirely lacking here. The young woman, though she has several lichenoid papules present, has, I believe, Fox-Fordyce disease.

DR. HERBERT RATTNER: Dr. Zakon showed this young man to a group of us about three weeks ago. At that time the lesions were classic noninflammatory discrete, firm small lesions in the axillae. Today they appear to be irritated, apparently from friction.

DR. STEPHEN ROTHMAN: The most striking feature in the second patient is the widespread involvement of areas supplied by apocrine glands outside the axillae, namely, perimamillary regions, linea alba, and pubes.

DR. S. J. ZAKON: I presented this second case, that of the woman, to prove the correctness of Dr. Cornbleet's statements that Fox-Fordyce disease tends to clear up during pregnancy. As a matter of fact, I thought this was one of the cases of which he spoke at the last meeting.

I presented the young man because Fox-Fordyce disease is extremely rare in males. Only about four or five cases have been reported. The French and the Germans consider Fox-Fordyce disease a form of neurodermatitis. The studies that Dr. Cornbleet and others have done in recent years prove that Fox-Fordyce disease is one of the endocrinopathies. Interesting was the fact that the young man failed to respond to x-ray therapy and antipruritics. The only relief that he obtained was from injections of male sex hormone, testosterone. How long one can continue such medication without doing damage, I do not know, but this patient's response proves that in Fox-Fordyce disease there is some disturbance of the gonadal secretions.

DR. THEODORE CORNBLEET: I do not think the Europeans hold a distinct view apart from ours that Fox-Fordyce disease is neurodermatitis. It is true that as late as 1917 Whitfield

thought that this American-described entity was a form of neurodermatitis, but nobody, as far as I know, has held to this view since the classic observations of Schiefferdecker on the apocrine glands in 1922. Any mention of neurodermatitis now in connection with apocrine disease is, I think, for historic purposes in a complete account.

DR. S. J. ZAKON: In Jadassohn's Handbuch (Berlin, Julius Springer, 1927, Vol. 6, p. 433) Fox-Fordyce disease is included in the chapter on neurodermatitis.

Leiomyoma. Presented by DR. IRENE NEUHAUSER.

W. M., a 45-year-old-white man, gives a history of having had brown spots on his arms and trunk since childhood. Fifteen years ago the spots began to enlarge and become red and painful. No new lesions have appeared since that time. He complains of paroxysmal pain which is worse at night and on pressure. The pain has become more intense in the past 10 months.

The patient states that his mother had the same type of painful lesions but that her mother and father and nine siblings were normal. The patient has no living children.

Examination shows multiple, movable, elevated nodules 0.5 to 1.5 cm. in diameter, ranging in color from pale pink to a dusky red, appearing on the middle third and lateral aspect of the right upper arm, with a few lesions on the lateral surface of the left forearm and left upper arm. There are also a few scattered lesions on the back and chest. The lesions show blanching after pressure.

The histologic examination revealed a tumor throughout most of the corium, composed of interlacing bundles of smooth muscle fiber running in various directions. Proliferating collagen bundles separate the muscle bundles. This is demonstrated well in the Van Gieson stain.

DISCUSSION

DR. IRENE NEUHAUSER: It is interesting to note that the condition of this patient was diagnosed as a schwannoma by the neuropathologists. Apparently this disease entity which is well known to the dermatologists is not recognized by the neurologists. At a recent meeting a case of leiomyoma with a similar familial history was presented, which makes one wonder if there may be some familial tendency in this disease. I have been asked to try and stimulate discussion in the hopes of finding some new therapy.

DR. M. R. CARO: Dr. Pace reported a case of leiomyoma before this Society a year or two ago in which he treated the condition with carbon dioxide snow locally with excellent results.

Adenoma Sebaceum. Presented by DR. DAVID OMENS, (by invitation) DR. HAROLD OMENS, and (by invitation) DR. STEFAN BIELINSKI.

Tuberculous Adenitis. Presented by DR. THEODORE CORNBLEET, (by invitation) DR. HENRY SCHORR, and (by invitation) DR. STEFAN BIELINSKI.

Scleroderma with Calcium Deposits in the Skin (Thibierge-Weissenbach Syndrome.) Presented by DR. JAMES WEBSTER, DR. SAMUEL BLUEFARB, and (by invitation) DR. STEFAN BIELINSKI.

Steatocystoma Multiplex. Presented by DR. JAMES WEBSTER, DR. SAMUEL BLUEFARB, and (by invitation) DR. J. F. SICKLEY.

Cutis Verticis Gyrata. Presented by DR. THEODORE CORNBLEET, DR. DAVID COHEN, and (by invitation) DR. J. F. SICKLEY.

Facial Granuloma with Eosinophilia. Presented by DR. R. M. OLIVER and DR. F. J. SZYMANSKI.

A Case for Diagnosis; Vesicular Eruption. Presented by DR. F. E. SENEAR and DR. J. B. HAEBERLIN, JR.

Periadenitis Mucosa Necrotica Recurrens Treated with Aureomycin Rinses. Presented by DR. STEPHEN ROTHMAN and (by invitation) DR. E. FARNEY-DAVIES.

A Case for Diagnosis (Folliculitis Ulerythematosa Reticulata?) Presented by DR. MICHAEL H. EBERT and (by invitation) DR. ALLEN S. PEARL, JR.

Xeroderma Pigmentosum, Mild Form. Presented by DR. STEPHEN ROTHMAN and (by invitation) DR. HAROLD M. SCHNEIDMAN.

Xeroderma Pigmentosum, Abortive Form (?). Presented by DR. STEPHEN ROTHMAN, (by invitation) DR. PETER L. BEAL, and DR. JOHN C. MURPHY.

Lichen Nitidus. Presented by DR. EUGENE LORANT (by invitation).

Nevus Unius Lateris. Presented by DR. STEPHEN ROTHMAN and (by invitation) DR. CALVIN J. DILLAHA.

Accidental Tattooing of the Face Treated by Abrasion with Sandpaper. Presented by DR. WILLIAM A. ROSENBERG.

Pemphigus Foliaceus. Presented by MILTON ROBIN.

Pemphigus with Ocular Involvement. Presented by DR. F. E. SENEAR and (by invitation) DR. H. C. SCHORR.

Lymphoblastoma. Presented by DR. STEPHEN ROTHMAN and (by invitation) DR. CALVIN J. DILLAHA.

Lichen Sclerosus et Atrophicus. Presented by DR. SAMUEL BLUEFARB and (by invitation) DR. MAX E. KLEIN.

Ulceration of the Skin Following Accidental Contact with Potassium Permanganate Tablets. Presented by DR. DAVID COHEN and (by invitation) DR. A. GOLDMAN.

SAN FRANCISCO DERMATOLOGIC SOCIETY

Stuart C. Way, M.D., *President*

Rees B. Rees, M.D., *Secretary-Treasurer*

Feb. 16, 1951

Acrokeratosis Verruciformis (Hopf). Presented by MAJOR JAMES DRAKE, M.C., U. S. A.

Captain W., a 43-year-old white nurse-anesthetist, first noted the present eruption on her hands and feet at the age of 23. However, she recalls that as a 6-year-old child she was taken to a physician because of excessive peeling of the feet unaccompanied by any inflammatory phenomena. Since the onset at 23 there has been no remission.

During the period from 1938 to 1940, the patient received an estimated total of about 1,500 r. to the hands and feet with no benefit.

She believes that her father has this same condition on the hands, and, on close questioning, it is probable that his eruption is of this general nature rather than eczematous.

Her general health has been good, with the exception of a three-year period when she was a Japanese prisoner-of-war during World War II. At that time she had malaria, amebic dysentery, and beri-beri. There are no known residua.

Results of a general physical examination were essentially normal. Examination of the skin reveals verrucous lesions, together with areas of a pearly mosaic appearance, located on the dorsal aspect of the distal portions of the fingers as well as on the ulnar borders and palmar aspects of the hands. Similar lesions are found on the plantar aspect of the feet, particularly along the medial sides. Remaining portions of the extremities, the face, and the trunk are spared.

DISCUSSION

DR. REES B. REES: This appeared to be hyperkeratosis with perhaps some deep-seated dyshidrotic vesiculation. There is relative absence of lesions on the backs of the hands and feet, and clinically these did not resemble either flat warts or common warts. Histologically there was no basket-weave appearance in the epidermis as is seen in epidermodysplasia verruciformis.

DR. MERLIN MAYNARD: Her father apparently had a similar condition, a fact which is in favor of acrokeratosis verruciformis. This patient had no lesions on the face, although such lesions are compatible with this diagnosis. One may see them on the ala of the nose occasionally. A few of her lesions resemble typical warts. When one sees an example of this condition and examines the individual lesion, it is hard to say whether that lesion is a wart or anything but a wart. However, I think this is a true acrokeratosis.

MAJOR JAMES DRAKE, M.C., U. S. A.: As regards vesicle formation, I am certain that none are present. The well-chosen descriptive clinical term "pearly mosaics" is well demonstrated in this patient. Microscopically the picture is one of acanthosis and pure hyperkeratosis.

A Case for Diagnosis (Progressive Pigmented Purpuric Disease?). Presented by DR. WALTER COLE (by invitation).

J. R., a 30-year-old Negro man, was born in Michigan of American parents and has resided in the United States all his life. At the age of 2 years he contracted smallpox, and at 15, acute gonococcal urethritis. He was in good health until 1947, when a pigmented pruritic papule developed over the upper third of the left tibia. During the ensuing two years this spread peripherally, appearing to progress by the development of discrete papules which later coalesced to form a plaque. As time passed, the pruritus disappeared, the pigmentation increased, and the involved area became rough. In 1948 a similar change occurred in the skin of the right leg. Further progression ceased in 1949.

Examination reveals bilaterally symmetrical, pigmented, hyperkeratotic plaques over the anterior aspects of the middle third of each tibia. The borders are atrophic, irregular in outline, and have outlying discrete lesions with a similar appearance. The hair follicles in the

involved epidermis present hyperkeratotic collars. Many of the central plugs are lost, producing a crater-like or punctiforme appearance. From a few of the craters atrophic hairs emerge. The changes in the follicles are most evident in the centers of the lesions, merging on the borders imperceptibly into normal hair-containing follicles. The plaque on the left leg measures 12 by 12 cm., and that on the right leg, 7 by 7 cm.

Laboratory investigation showed a normal red blood count, normal leucocyte count, and normal differential count. The reaction to a serologic test for syphilis was negative. Results of urinalysis were normal.

An excision biopsy through the center of one of the involved areas was done, and the slide is presented. It shows hyperkeratosis without parakeratosis, follicular plugging, loss of rete pegs, an intact basal-cell layer separated from a dense band-like round-cell infiltrate in the upper corium by a clear zone of collagen. In the mid corium are many dilated blood vessels, with some hemorrhage and scattered clumps of pigment.

DISCUSSION

DR. STUART WAY: I think this is an example of porokeratosis vera. It is not typical of the Mibelli type. The pathology is not typical for the latter type, and the clinical picture varies.

DR. FRANCES TORREY: One hesitates to make a diagnosis of a condition which one has seen only in illustrations. Members of the resident staff of the University of California have looked through the literature on this subject but find no details regarding porokeratosis vera. When this is compared histologically with findings in porokeratosis of Mibelli there are different features. In this condition there is an increased inflammatory reaction and a definite separation of the inflammatory zone from the epidermis, which is not characteristic of the Mibelli type. I would be happy to hear this case discussed by someone who has seen porokeratosis vera. There was one case presented by Dr. Nelson Paul Anderson last year.

DR. EUGENE FARBER: This is a unique condition. I have never seen anything like it. There appears to be some suggestion of delling clinically, as well as a Grenz zone microscopically. One should have a connective-tissue stain to see whether there is normal or abnormal fibrous tissue and whether there is sclerosis of the collagen. I have never heard of porokeratosis associated with hemosiderosis. Perhaps the latter feature here is traumatic in origin. The capillary and arteriolar changes are not great enough to warrant calling this primarily a hemosiderosis on the basis of vascular changes. Lichen sclerosis et atrophicus would be a guess on the basis of the delling, the tissue-paper crinkling of the skin in some areas, and the suggestion of the Grenz zone microscopically. I would like to see a deep-excision biopsy performed with connective tissue stains, such as elastin, Van Gieson, and Mallory.

DR. KEMP DOWDY: This eruption suggested hypertrophic lichen planus to me. It has features of this disease, both clinically and histologically.

DR. FREDERICK NOVY JR.: In the history the blood findings are said to be normal. I would suggest further and frequent blood studies with the thought of an early atypical sickle-cell anemia change in the skin. This is a bizarre picture, and clinically it could be an unusual lichen planus.

DR. WALTER COLE (by invitation): When we first examined this patient we considered the diagnosis of porokeratosis vera non perstans as illustrated in Nekam's text (Corpus Iconum Morborum Cutaneorum, Leipzig, Johann Ambrosius Barth, 1938, Fig. 3035). That illustration is a double for this one. In this case which was described by Schmidt, there was a transient condition occurring in a miner and healing spontaneously. Dr. Nelson Paul Anderson reported a case of porokeratosis punctiforme in the ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY (**61**: 505 [March] 1950) in the transactions of the Los Angeles Dermatological Society. The histologic findings of this case were not included in the manuscript. Subsequently, on finding that the histologic features did not fit the picture of porokeratosis Mibelli, we considered progressive pigmentary dermatosis, pigmented purpuric lichenoid dermatitis, etc. Histologically the picture does not fit these conditions either; there is no loss of a granular layer, nor is there a para-

keratosis as one should see in pigmented purpuric lichenoid dermatitis. I am sorry that we have not done a cholesterol estimation of the blood, because in several cases of progressive pigmentary dermatosis hypercholesteremia has been demonstrated (Schamberg, Templeton, Becker). Histologically this does not fit the picture of lichen planus. There is no "washing out" of the basal-cell layer, etc. We do not know the nature of the clear zone between the dense band-like infiltration and the epidermis. Further staining technics to demonstrate connective tissue will be done.

A Case for Diagnosis (Insect Bite Reaction? Prurigo Nodularis?). Presented by MAJOR SANFORD VAUGHAN, M.C., U. S. A. (by invitation).

W. K., a 30-year-old soldier, received numerous insect bites while on maneuvers in the Canal Zone in April, 1950. Two weeks later he noted an abrupt onset of discrete, intensely pruritic, firm nodules over the trunk and extremities. These nodules have persisted unchanged since that time and have failed to respond to locally applied soothing ointments and lotions, penicillin, aureomycin, and tripelennamine (pyribenzamine®). He was transferred to Letterman Army Hospital with a diagnosis of prurigo nodularis. No treatment has been instituted thus far. A biopsy of one of the nodules was done, and a slide is presented.

DISCUSSION

DR. ROBERT STEWART: Since his return to this country and the absence of new insect bites, he has had recurrent lesions and new lesions. Because of the granulomatous histologic picture with giant-cell formation, one should consider a mycotic infection. Serial sections might be performed with cultures and animal inoculation of new biopsy material also.

DR. FREDERICK NOVY JR.: What mycotic infection would you consider?

DR. ROBERT STEWART: I do not know. This man was in the Canal Zone, and there may be mycotic infections other than those we commonly see here, which would account for this unusual picture.

DR. HERMAN ALLINGTON: I believe that these lesions are chronic granulomatous reactions to the bites of ticks or other insects from the Canal Zone. He has been back in this country for only two or three days. He insists that he has actually picked as many as a dozen ticks at a time from his skin. I have seen a man just recently who has had many flea bites, a few of which have become persistent papular reactions such as these.

DR. HERBERT JOSEPH: It would be of interest to do intradermal skin tests with flea antigen to see if a granulomatous reaction would result. It may be possible to prepare a tick antigen also.

DR. KEMP DOWDY: This man has a tendency toward keloid or hypertrophic scars, as is evidenced from old lacerations present. One wonders, therefore, if he does not tend to react in an exaggerated fashion to insect bites and other injuries as well.

DR. MERLIN MAYNARD: I agree that this is a reaction to an insect bite. Perhaps a portion of the tick's mandible has been left in the individual wound. A true prurigo shows more wrinkling and pigmentation and hairgrowth. In contrast, these lesions are similar to the postscabetic nodules that we see occasionally. When I first saw this patient I considered the possibility of a papulonecrotic tuberculid, but more careful scrutiny ruled this out.

DR. JOHN SKAHEN (by invitation): Dr. Arthur Allen has described pseudoepitheliomatous hyperplasia, with a polymorphous infiltrate, predominantly polymorphonuclear leucocytes with some eosinophiles, in granulomatous reactions to insect bites. The chief infiltrating cell here is monocytic in character. In addition, there is no fibrosis here. Furthermore, the reaction in this case is superficial.

DR. REES B. REES: Perhaps some of you may remember the case that was presented at the histologic session of the California Medical Association meeting last year. The features histologically were similar to those found in this case, with a nest of inflammatory cells which even suggested a lymphoma.

DR. HERMAN ALLINGTON: These lesions may respond to treatment with liquid nitrogen.

MAJOR SANFORD VAUGHAN, M.C., U. S. A. (by invitation): I spent some time in Panama myself and in 1940 manifested a somewhat similar prurigo. Although I had only six to eight lesions, they were intensely pruritic and lasted over a year. At the time I attributed them to some form of insect bites, probably from ticks brought in on the fur of a kitten I had which played in the jungle grass nearby.

A Case for Diagnosis (Erythroderma Congenitale Ichthyosforme? Ichthyosis?). Presented by DR. JULIAN LUNSFORD.

Trichoptilosis (Fragilitas Crinium). Presented by DR. ROBERT WALTON (by invitation).

Scleroderma. Presented by DR. ALBERT SHUMATE and DR. EUGENE FARBER.

Neurodermatitis with Seborrheic Component Unsuccessfully Treated with Corticotropin. Presented by DR. ROBERT WALTON (by invitation).

A Case for Diagnosis (Purpuric Lichenoid Dermatitis of Gougerot-Blum? Schamberg's Peculiar Progressive Pigmentary Dermatosis? Angioma Serpiginosum?). Presented by DR. MORTIMER FALK.

Rhinoscleroma? Presented by DR. ARNE INGELS.

Mercury Sensitivity in an Area of Tattoo. Presented by DR. NORMAN EPSTEIN and DR. JAMES ALLEN.

News and Comment

ANNOUNCEMENTS

New Dermatological Journal.—"With the hope that Australia might have something to add to dermatology as a whole—to provide the opportunity and to stimulate Australian dermatologists to report their experiences—to create for Australia an increased stature in world dermatology—to bring members into closer association with colleagues overseas—"

With these commendable aims the first issue of the *Australian Journal of Dermatology*, sponsored by the Dermatological Association of Australia, appeared in March, 1951. It promises a bright future. The A. M. A. ARCHIVES extends a warm welcome to the new journal and wishes for Dr. Adrian M. Johnson, the editor, and the members of his editorial board high success in their venture and complete fulfillment of their hopes. The journal asks for and merits the active support of American dermatologists.

Section on Dermatologic Allergy.—The American College of Allergists, at their annual meeting in Pittsburgh, April 7 to 9, 1952, will have a Section on Dermatologic Allergy. Anyone wishing to present a paper at this Section should communicate with Dr. Adolph Rostenberg Jr., University of Illinois College of Medicine, 1853 W. Polk St., Chicago 12.

Space Available in Scientific Exhibit at Chicago.—Space is available in the Dermatological Section of the Scientific Exhibit of the American Medical Association, June 9 to 13, 1952. Applications for space should be sent immediately to Dr. James R. Webster, 122 S. Michigan Ave., Chicago 3.

Obituaries

WILL CHARLES DAVIS, M.D.
1913-1951

Will Charles Davis died June 23, 1951. He is survived by his widow and two children.

He was born in Portland, Ore., on March 31, 1913, and was graduated from the University of Oregon Medical School in 1939. He was a member of Alpha Omega Alpha, Nu Sigma Nu, and Kappa Sigma fraternities. His dermatologic training consisted of a residency at the University of Oregon Medical School and a fellowship at Mayo Foundation. He was certified by the American Board of Dermatology and Syphilology by examination in 1947. Shortly before his death he was promoted to the position of Assistant Clinical Professor of Dermatology at the University of Oregon Medical School.

Dr. Davis practiced dermatology and syphilology in Portland, Ore., starting in 1944. Because he possessed a keenly analytical mind and a sympathetic interest in the problems of others, his success was quickly assured. His genial personality and heart-warming friendship charmed everyone.

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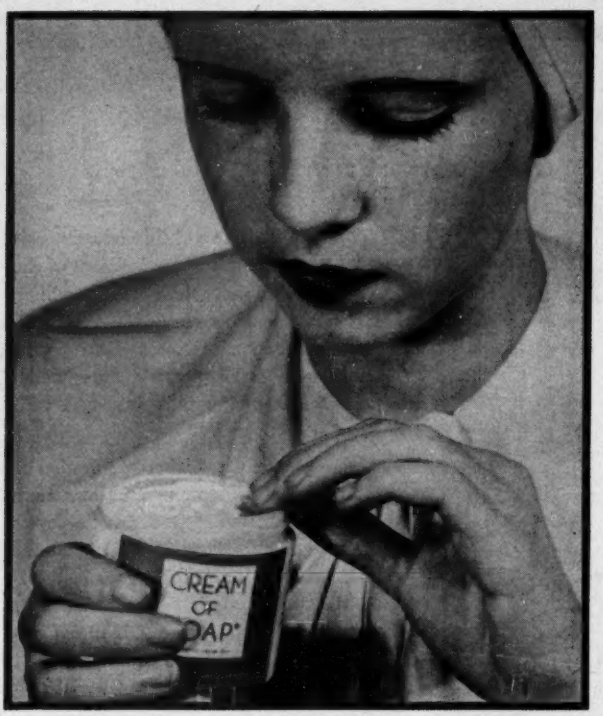

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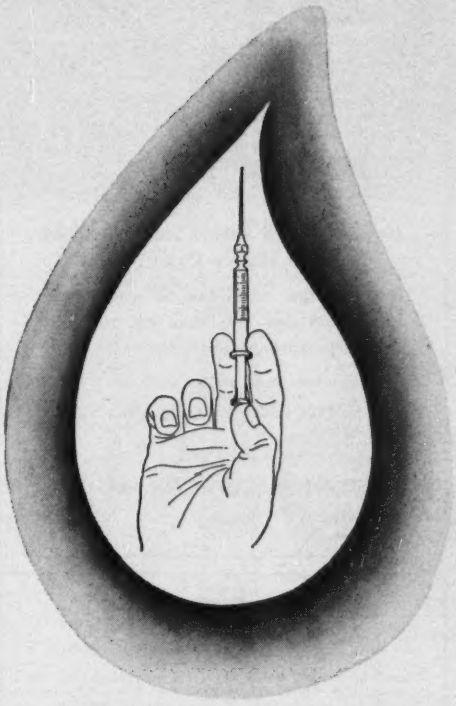

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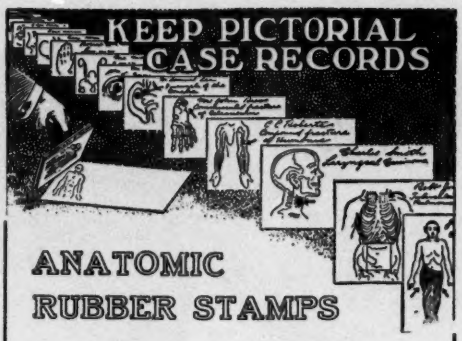

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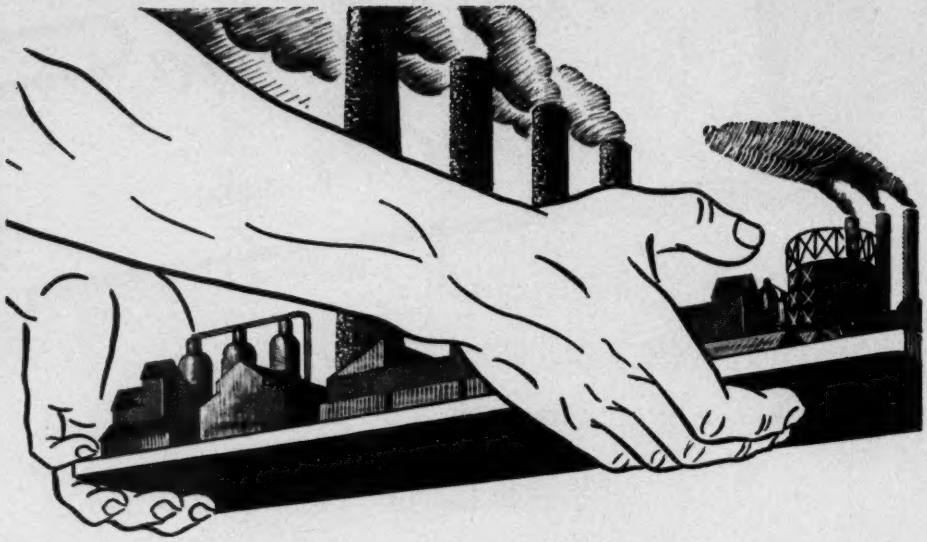

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